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ELUCIDATING THE FUNCTIONAL NEURAL CORRELATES OF EMOTIONAL FACE PROCESSING DEFICITS IN BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA

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ELUCIDATING THE FUNCTIONAL NEURAL CORRELATES OF EMOTIONAL FACE PROCESSING DEFICITS IN BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA

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ABSTRACT

Frontotemporal dementia is a devastating neurodegenerative disorder consisting of progressive focal atrophy of the prefrontal and temporal lobes. Emotional facial expression deficits are widely acknowledged in behavioural variant frontotemporal dementia (bvFTD) and are speculated to partially account for patients' social-cognitive deficits. To our knowledge this is the first study to delineate the functional neuroanatomy of facial expression processing in bvFTD using functional MRI, while controlling for voxel-wise atrophy. The results indicate emotion-specific functional abnormalities in frontotemporal regions in patients with bvFTD. BvFTD patients also demonstrated decreased activity in posterior ventral visual regions, perhaps suggesting reduced input from anterior frontal and limbic regions. Finally, bvFTD was associated with increased activity in the dorsal attentional network, providing some of the first evidence of a potential compensatory response for functional deficits in frontotemporal regions. Together these findings suggest that functional MRI combined with tasks targeting social-cognitive deficits is a powerful technique to quantify neural systems involved in emotion processing in bvFTD.

Keywords: frontotemporal dementia; functional magnetic resonance imaging; facial expressions; empathy

CO-AUTHORSHIP

All thesis aspects were completed by Karim Virani except for the following:

My supervisors, Dr. Elizabeth Finger and Dr. Derek Mitchell, contributed throughout my thesis. Dr. Finger was responsible for patient and healthy control recruitment and assisting in neuroimaging data acquisition. Both Dr. Finger and Dr. Mitchell contributed to the experimental design, data analysis and interpretation, and manuscript preparation.

Kim Krueger was the MRI technologist for the majority of the study.

Sarah Jesso and Sarah Ross conducted neuropsychological testing of participants at the Cognitive Neurology and Alzheimer Research Centre at St. Joseph's Hospital.

DEDICATION

To my parents,
who have relentlessly supported all of my endeavours.

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ABBREVIATIONS

AFNI	Analysis of functional neuroimages
ANART	American national adult reading test
BA	Broadmann's area
BET	Brain extraction tool
BOLD	Blood-oxygen-level-dependent
bvFTD	Behavioural variant frontotemporal dementia
CNARC	Cognitive neurology and Alzheimer research centre
CSF	Cerebrospinal fluid
CT	X-ray computed tomography
EPI	Echo planar imaging
FAST	FMRIB's Automated Segmentation Tool
FBI	Frontal behavioural inventory
FLIRT	FMRIB's linear image registration tool
fMRI	Functional magnetic resonance imaging
FSL	FMRIB software library
FTD	Frontotemporal Dementia
FWHM	Full width at half maximum
GM	Grey matter
MMSE	Mini-mental state examination
MNI	Montreal neurological institute
MRI	Magnetic resonance imaging
NA	Not applicable
PET	Positron emission tomography
ROI	Region of interest
SD	Semantic deficits
SPECT	Single-photon emission computed tomography
Tim	Total imaging matrix
WCST	Wisconsin card sorting test
WM	White matter

CHAPTER 1

Introduction

1.1 Frontotemporal dementia background

The increase in age and proportion of older persons has been coupled with an augmentation of age-related illnesses, specifically neurodegenerative diseases (Arvanitakis, 2010). In 1892, a neuropsychiatrist from Prague named Arnold Pick first described a patient presenting with progressive language and behavioural abnormalities while demonstrating definitive left temporal lobe atrophy post-mortem (Pick, 1892). This marked the initial case of "Pick's disease". Soon after, Alois Alzheimer, a German psychiatrist and neuropathologist, discovered the presence of accumulated neuronal protein complexes in atrophied cortex (Alzheimer, 1911). He called his molecular finding "Pick's bodies", which later became associated with Pick's disease. Accompanying our increased nosology of Pick's disease over the last century has been a change in nomenclature to the now widely accepted "frontotemporal dementia" in order to better represent the heterogeneity in disease manifestation and progression. Frontotemporal dementia (FTD) is a devastating neurodegenerative disorder consisting of progressive, circumscribed focal atrophy of the prefrontal and temporal lobes (Lund-Manchester, 1994; Neary, 1998), resulting in striking personality and behaviour changes. FTD has been postulated to be the third most prevalent neurodegenerative dementia (behind Alzheimer's disease and Lewy body disease) and the second most prevalent (behind Alzheimer's disease) when disease onset precedes the age of 65 (Arvanitakis,

2010; Neary et al., 1998). Presently, there is no available cure for FTD, nor any symptomatic or modifying treatment demonstrating substantial efficacy.

1.2 Clinical variants of frontotemporal lobar degeneration

Behavioural variant FTD (bvFTD) is the most common clinical subtype of frontotemporal lobar degeneration. Less common subtypes include semantic dementia and progressive non-fluent aphasia, which are both language-impairing clinical subtypes. Briefly, progressive non-fluent aphasia presents as a language expression deficit, resulting in effortful speech production despite adequate language understanding (Snowden et al., 1996). In comparison, semantic dementia features impairment of semantic knowledge relating to verbal and nonverbal concepts (Hodges et al., 1992; Kertesz et al., 2010; Snowden et al., 1996).

1.3 Clinical criteria of bvFTD

BvFTD is characterized by striking changes to social behaviour and personality relative to the pre-morbid state. The core diagnostic features of bvFTD according to the Neary Criteria, include an insidious onset and gradual disease progression, early deficits in interpersonal conduct, early behavioural dysregulation, apathy, and loss of insight (Neary et al., 1998). Secondary clinical symptoms (not necessary for but may supplement diagnosis) include difficulty in modulating behaviour (e.g. stereotyped and perseverative behaviours, impulsiveness, mental inflexibility, inattentiveness, and utilization behaviours), inappropriate behaviours (e.g. hypersexuality, hyperorality, dietary alterations, and declining personal hygiene), and altered speech patterns (e.g.

economy of speech, press of speech, stereotypy, echolalia, perseveration, and mutism; Neary et al., 1998). Despite abnormalities in social cognition and personality, bvFTD patients are relatively spared in language, memory, and visuospatial functioning (Graff-Radford and Woodruff, 2007; Kertesz, 2008; Lund-Manchester, 1994; Neary et al., 1998, 2005). In addition to meeting Neary Criteria, additional neuroimaging evidence (MRI, CT, or SPECT) must be present for bvFTD diagnosis, consistent with the new FTD consensus criteria (Rascovsky et al., 2010).

1.4 Heterogeneity in FTD phenotype

Instead of viewing the FTD subtypes as independent disease entities, research now supports an FTD syndrome theory with heterogeneous clinical and pathological symptomatology. Patients presenting with symptoms of one FTD clinical subtype can progress to develop symptoms of other subtypes (Arvanitakis, 2010; Graff-Radford and Woodruff, 2007; Kertesz et al., 2007; McKhann et al., 2001; Snowden et al., 2007), referred to as 'secondary' or even 'tertiary syndromes'. Kertesz et al. (2007) followed 319 FTD patients prospectively and determined that approximately two-thirds developed additional FTD syndromes. Similar behavioural and emotional symptoms frequently co-occur in FTD patients who show semantic dementia symptoms (Hodges et al., 1992; Kertesz et al., 2007; Rosen et al., 2002a; Snowden et al., 1992), including severe difficulties in naming and word comprehension (predominantly nouns), empty spontaneous speech occurring in the presence of preserved speech fluency, syntax, and phonology (Hodges et al., 1992; Snowden et al., 1989, 1992; Warrington, 1975). Semantic dementia has been referred to as the "What is…?" disease, due to the high

proportion of patients questioning the meaning of words (e.g. "What is steak?"; Kertesz, 2010).

1.5 Demographics

In general, the onset age of bvFTD has been estimated to be between 40 to 75 years (Kertesz, 2008; Neary, 2005), with an average specific onset of about 59 years (Garcin et al., 2009). BvFTD has been estimated to have an earlier age of onset in comparison to other dementias, such as Alzheimer's disease, which has an onset in the early 70's (van der Flier, 2011). The average duration of the FTD disease course is about 6.5-8.5 years, with a delay of approximately 3 years from symptom onset to diagnosis (Garcin et al., 2009), during which irreversible neuronal loss progresses. Population studies indicate a relatively equal distribution of FTD between sexes (Rosso et al., 2003; Snowden et al., 1996). FTD has been shown to be a heritable neurodegenerative disease, with up to 40% of FTD patients showing positive family history (Rohrer et al., 2009b).

1.6 Neuropathology

FTD is associated with the abnormal accumulation of neuronal proteins and neuronal loss, which likely begins decades prior to the initial manifestation of clinical symptoms (Finch et al., 2009; Rohrer et al., 2009a). This results in selective, but progressive, loss of brain function and tissue in the frontal and temporal lobes. The presenting clinical phenotype in frontotemporal lobar degeneration is hypothesized to be determined by the focalized frontotemporal neuronal atrophy patterns (Arvanitakis, 2010). Neuropathological assessment and structural neuroimaging (CT or MRI) has

associated bvFTD symptomatology with circumscribed degeneration of the prefrontal and anterior temporal lobes, bilaterally, commonly right hemisphere greater than left (Boccardi et al., 2005; Davitzikos et al., 2008; Eslinger et al., 2007; McKhann et al., 2001; Neary et al., 2005; Pereira et al., 2009; Perry and Miller, 2001; Rabinovici et al., 2007; Rosen et al., 2002a; Short et al., 2005; Snowden et al., 2007; Varma et al., 2002). Specifically, early bvFTD atrophy is targeted to a frontal paralimbic network, including the anterior cingulate cortex, anterior insula, frontal pole, amygdala, and striatum, with frequent right hemisphere asymmetry (Seeley, 2008). In patients who develop semantic deficits in addition to behavioural and personality symptoms, atrophy is commonly observed bilaterally in the temporal poles, amygdala, ventromedial prefrontal cortex, insula, and inferoposterior temporal regions (Rosen et al., 2002a; Seeley et al., 2005). By assessing patterns of grey matter loss using voxel-based morphometry, the following four distinct anatomical subtypes have recently been proposed in bvFTD: temporal-dominant, temporofrontoparietal, frontotemporal, and frontal-dominant subtypes (Whitwell et al., 2009).

1.7 Functional neuroimaging

Functional neuroimaging is commonly used as an adjunct in bvFTD diagnosis to index the integrity of the frontal and temporal lobes when clinical symptomatology is at an early stage and structural scans show mild (or no) atrophy (Foster et al., 2007; Graff-Radford and Woodruff, 2007; McNeill et al., 2007; Neary et al., 2005). Previous studies using PET or SPECT reported glucose hypometabolism and hypoperfusion, respectively, in prefrontal and/or anterior temporal lobes (Diehl-Schmid et al., 2007a; Graff-Radford

and Woodruff, 2007; Hodges et al., 1992; Jeong et al., 2005; McKhann et al., 2001; McMurtray et al., 2006; McNeill et al., 2007; Mendez et al., 2006; Miller et al., 1997; Salmon et al., 2003; Talbot et al., 1998; Varma et al., 2002). Functional magnetic resonance imaging (fMRI) has just recently been used to assess the functional connectivity of large-scale neural networks in neurodegenerative diseases. Resting-state fMRI has demonstrated that specific neurodegenerative diseases (e.g. bvFTD, Alzheimer's disease, and semantic dementia) target individual large-scale neuronal networks (Seeley et al., 2009). More precisely, bvFTD shows reduced functional connectivity within an anterior 'salience network' (responsible for adaptive social-cognitive processes), composed of an anterior cingulate cortex and orbital frontoinsula network. Interestingly, bvFTD shows increased connectivity within a posterior 'default mode network' (responsible for episodic memory and visuospatial functions), composed of a posterior hippocampal-cingulo-temporal-parietal network, regions actually vulnerable to atrophy in Alzheimer's disease (Seeley et al., 2007; Zhou et al., 2010). It has been postulated that the clinical phenotypes associated with distinct neurodegenerative diseases are partly accounted for by functional changes within large-range neuronal networks (Seeley et al., 2010).

To our knowledge, the only previous FTD study to couple fMRI and a cognitive task investigated neuronal functioning associated specifically with working memory. FTD patients demonstrated decreased activation relative to Alzheimer's patients within a working memory network, including frontal cortical regions (Rombouts et al., 2003). However, working memory impairment is not a direct cognitive symptom in bvFTD, and working memory problems are not a core feature of the disorder (Neary et al., 1998). No

study has yet combined functional neuroimaging and cognitive tasks targeting the core diagnostic social-cognitive deficits in bvFTD.

1.8 Face processing

1.8.1 Importance of processing facial emotion

Facial expressions have long been recognized as a critical social cue for directing appropriate interpersonal behaviours (Darwin, 1872). The ability to successfully recognize emotion from faces in our environment is absolutely critical for social behaviour, especially empathic behaviour (Blair, 2003). Impairment in facial expression recognition, particularly expressions conveying negative valence such as fear and anger, is associated with inappropriate social behaviours (Blair and Cipolotti, 2000; Blair et al., 2004; Corden et al., 2006; Marsh and Blair, 2008). In addition, accurate identification of fearful expressions can even predict prosocial behaviours (Marsh et al., 2007). One of the defining symptoms in bvFTD, independent of semantic impairment, is a lack of empathy for others, even immediate family members (Kertesz et al., 2000; Rankin et al., 2006). A reduction in empathy in bvFTD patients is believed to be partially accounted for by impairments in facial expression processing (Diehl-Schmid et al., 2007b; Lough et al., 2006); however, neural substrates associated with emotional face processing have yet to be delineated in bvFTD.

1.8.2 Facial expression processing in FTD

Recognition of emotional faces has previously been shown to successfully differentiate mild bvFTD from healthy controls. Patients with mild bvFTD show deficits

in both positive and negative facial emotion recognition (Diehl-Schmid et al., 2007b). Compared to mild Alzheimer's disease patients, who performed at control levels, bvFTD patients showed a difficulty in recognizing negative emotions (Fernandez-Duque and Black, 2005; Lavenu et al., 1999). Negative facial emotions are believed to be more difficult to recognize than positive ones (Russell, 1994), raising the issue of task difficulty potentially confounding patient performance. However, bvFTD patients have previously shown difficulty in recognizing both angry and fearful faces, the former understood to be easier to recognize than the latter (Fernandez-Duque and Black, 2005). Despite definitive expression processing deficits, bvFTD patients have shown preserved general face processing abilities, such as facial identity discrimination (Rosen et al., 2002b, 2004), facial familiarity judgment (Keane et al., 2002), and gender discrimination (Fernandez-Duque and Black, 2005).

BvFTD patients with predominant frontal lobe atrophy show deficits in the recognition of both facial and vocal emotions, supporting a generalized emotion processing impairment independent of sensory modality (Keane et al., 2002). BvFTD patients with predominant temporal lobe atrophy are specifically vulnerable to emotion processing deficits as atrophy is commonly concentrated in the amygdala, anterior temporal lobes, and orbital frontal cortex, regions believed to play crucial roles in emotional stimulus processing (Rosen et al., 2002b). Temporal-dominant bvFTD patients have shown deficits in the processing of negative emotions, despite demonstrating preserved happy emotion processing (Rosen et al., 2002b). Comparisons between frontal-dominant and temporal-dominant bvFTD patients have demonstrated impaired negative expression processing in both subtypes; however, frontal-dominant

bvFTD patients also showed difficulty processing happy faces, suggesting a more widespread facial expression processing deficit in this subtype (Rosen et al., 2004). It is important to note this finding remains controversial. For example another study reported preserved happy expression recognition processing in patients with frontal-dominant bvFTD (Lough et al., 2006).

1.8.3 Neural substrates of facial expression processing

The neural architecture of face perception has been studied in both healthy and lesion populations. Utilizing fMRI, Kanwisher et al. (1997) demonstrated that the fusiform face area, located within the fusiform gyrus, shows enhanced activation to faces relative to common objects. Functional neuroimaging studies in humans have shown increased activation in ventral visual regions, specifically fusiform cortex, in response to emotional compared to neutral facial expressions (Amting et al., 2010; Fusar-Poli et al., 2009; Morris et al., 1998; Pessoa and Ungerleider, 2004; Vuilleumier et al., 2001), and to faces depicting high relative to low emotional intensity (Surguladze et al., 2003). Research suggests that projections from the amygdala modulate activity in the ventral visual stream, enhancing neural representation in fusiform cortex for stimuli with emotional salience (Amaral et al., 1992; Vuilleumier et al., 2001, 2004). Patients with mesial temporal lobe sclerosis with both hippocampal and amygdala damage fail to show augmented fusiform activation in response to fearful faces; however, similar patients with sclerotic damage restricted to the hippocampus, sparing the amygdala, show increased fusiform activity during fearful face processing (Vuilleumier et al., 2004). In comparison to the amygdala, which processes crude, low resolution facial aspects, the fusiform

activates most robustly to facial features in higher frequency resolution (Vuilleumier et al., 2003). The data are consistent with the idea that facial processing is associated with a spatially distributed neural network and emotion processing can modulate neural representation of faces in the ventral visual stream, specifically fusiform cortex.

In addition to outlining neurofunctional regions involved in face processing generally, specific neural regions have been associated with the healthy processing of individual facial expressions which are notably also regions affected by FTD pathology.

1.8.3.1 Angry faces

Functional neuroimaging studies have reported medial prefrontal/anterior cingulate cortex (Blair et al., 1999; Harmer et al., 2001), and ventrolateral prefrontal cortex (inferior frontal gyrus; Blair et al., 1999; Fusar-Poli et al., 2009) to be associated with angry expression processing. Angry faces signal to the observer the requirement of behaviour modification (Blair and Cipolotti, 2000; Blair et al., 1999; Mitchell, 2011), and ventrolateral prefrontal cortex appears to be active during this general process – when an environmental cue signifies the modification of a behavioural response (as reviewed in Mitchell, 2011). In addition to processing facial expressions of anger, increased activity in ventrolateral prefrontal cortex has been associated with behaviour modification in response to social cues (Finger et al., 2006; Marsh et al., 2009).

1.8.3.2 Disgusted faces

Defined as "bad taste", Darwin acknowledged that disgust refers to repulsion-eliciting environmental stimuli (Darwin, 1872). FMRI has associated disgusted facial

expression processing with activation of the insula and basal ganglia (Fusar-Poli et al., 2009; Kipps et al., 2007; Phillips et al., 1997; Sprengelmeyer et al., 1998). Interestingly, processing of vocal disgust expressions failed to elicit significant activation of these regions (Phillips et al., 1998). Insula activation in response to disgusted facial expressions may reflect the awareness of another's gustatory processing (Jabbi et al., 2007). Moreover, reduced sensitivity to disgust, measured by a disgust personality questionnaire, has been associated with decreased blood-oxygen-level dependent (BOLD) signal, measured via fMRI, in anteroventral insula upon viewing disgusting foods (Calder et al., 2007), demonstrating the association between insula functioning and disgust related sensitivity.

1.8.3.3 Fearful faces

Lesion studies have highlighted the amygdala as a central region involved in the processing of fearful expressions. Patients with bilateral amygdala injuries demonstrate impairment in recognizing negative facial emotions, most pronounced for fear (Adolphs et al., 1999). Functional neuroimaging studies, both PET and fMRI, have consistently demonstrated increased regional cerebral blood flow and increased BOLD signal, respectively, in the amygdala during fearful expression processing (Fusar-Poli et al., 2009; Morris et al., 1996, 1998, 2002; Pesoa et al., 2002; Phillips et al., 1998). Previous work has reported a lesion patient with bilateral focal amygdala damage, demonstrating fear recognition deficits, who failed to fixate on the eye region during face recognition tasks; however, recognition was at control levels when explicitly directed towards the eyes (Adolphs et al., 2005). Amygdala activity has also been shown to predict an

observer's eye gaze shifts towards the eyes of a fearful face (Gamer and Buchel, 2009); thus, supporting the importance of eye regions when processing fearful faces (Adolphs, 2008). This data also supports the role of the amygdala in directing attention towards salient features of environmental social cues, for example, during threatening stimuli evaluations. In addition to the amygdala, increased activation in the medial frontal gyrus has been associated with fearful expression processing (Fusar-Poli et al., 2009).

1.8.3.4 Happy faces

Previous neuroimaging studies have associated happy expression processing with increased activation in the amygdala (Fusar-Poli et al., 2009; Kipps et al., 2007; Pessoa et al., 2002) and rostral anterior cingulate/ventromedial prefrontal cortex (Fusar-Poli et al., 2009). Increased activity in ventromedial prefrontal cortex has also been associated with representing reward values of stimuli (as reviewed in Mitchell, 2011), such as pleasant tastes and smells (de Araujo et al., 2003; Gottfried et al., 2002; O'Doherty et al., 2001) and pleasant visual pictures (Dolcos et al., 2004). Difficulties recognizing happy expressions are not always reported following lesions to the amygdala and ventromedial prefrontal cortex (Lough et al., 2006; Rosen et al., 2002b), perhaps due to the ease with which these expressions can be identified.

1.8.3.5 Sad faces

Neural correlates implicated in the processing of sad expressions have been variable across studies. A previous PET study demonstrated hypermetabolism in the amygdala and temporal pole during sad expression processing (Blair et al., 1999). While

viewing sad film excerpts, healthy females demonstrated activation in the anterior temporal pole, midbrain, amygdala, insula, and ventrolateral prefrontal cortex (Levesque et al., 2003). FMRI studies in healthy adults correlated the processing of sad expressions with increased amygdala activation (Fusar-Poli et al., 2009). The amygdala has been recognized to have a prominent role in emotional learning (LeDoux, 1998), where sad expressions represent unconditioned stimuli (Blair et al., 1999). Aversive conditioning to sad expressions is believed to be essential for healthy moral development (Blair, 1995). Further supporting the involvement of the amygdala in sad processing, a reduced autonomic responsiveness to sad expressions, compared to controls, has been reported in individuals with psychopathy, a disorder associated with amygdala dysfunction (Blair et al., 1997).

1.8.4 Neural correlates of emotional face processing in FTD

The primary neural regions subject to atrophy in bvFTD parallel the regions previously implicated in the healthy processing of emotional facial expressions. As such, pathology in frontotemporal regions associated with emotion-specific facial expression processing can also partially account for bvFTD symptomatology. For example, ventrolateral prefrontal cortical atrophy, involved in angry expression processing, has also been correlated with inappropriate social behaviours in FTD (Massimo et al., 2009). FTD patients' dysfunction in this neural region has been associated with deficits in modifying behaviour in response to task rules (Rahman et al., 1999), a likely partial explanation for abnormal social behaviours in FTD. Insula dysfunction in bvFTD may be related to the insensitivity towards disgusting social cues (e.g. disgusted faces) and

disgust-inducing environmental stimuli (e.g. rotten food; Ikeda et al., 2002). Anterior temporal cortex, specifically the amygdala, and medial frontal regions have not only been previously implicated in the processing of fearful, happy, and sad faces, but also considered to be involved in experiencing empathic behaviours towards stressful or upset individuals (as reviewed in Decety and Jackson, 2004). Previous studies have correlated a lack of empathy in bvFTD to structural atrophy in anterior temporal and medial frontal cortex (Decety and Jackson, 2004; Eslinger et al., 2011; Kipps and Hodges, 2006).

Prior studies of the neural correlates of facial expression processing in FTD focused exclusively on atrophy correlations, with limited results. For example, negative expression recognition deficits in frontotemporal lobar degeneration have been correlated with right inferolateral temporal cortex atrophy (Rosen et al., 2006) and angry faces with posterior insula (Omar et al., 2010). Structural atrophy and facial expression recognition correlations appear insensitive in dissociating frontal-dominant and temporal-dominant FTD patients (Omar et al., 2010).

1.9 Thesis hypotheses

Despite the established behavioural impairment in recognizing facial expressions, the functional neuroanatomy of facial expression processing has yet to be delineated in bvFTD. We have applied fMRI, while correcting for measurable atrophy, to index the functional neural correlates in bvFTD patients during the processing of emotional facial expressions. We hypothesized bvFTD patients would demonstrate decreased BOLD signal in frontotemporal regions that are both directly affected by FTD pathology and essential for facial expression processing. Specifically, we predicted bvFTD patients

would demonstrate decreased activation relative to controls in ventrolateral prefrontal cortex (inferior frontal gyrus) when processing angry expressions, in the amygdala during fearful expressions, and in the insula during disgusted expressions. Next, we predicted fMRI will demonstrate functional differences between bvFTD patients without semantic deficits and those with semantic deficits; specifically, bvFTD patients without semantic deficits would show reduced frontal activation during angry and disgusted faces and bvFTD patients with semantic deficits would demonstrate reduced activation in anterior temporal lobe regions, such as the amygdala, during the processing of fearful, happy, and sad expressions. In addition, due to functional abnormalities in limbic regions, we hypothesized bvFTD patients would show secondary reduction in BOLD signal in regions downstream from limbic system structures and not typically affected in FTD, but perform a fundamental role in general face processing, such as fusiform cortex. Lastly, detected neural dysfunction was predicted to survive voxel-wise grey matter atrophy correction, providing support for the notion that anomalous changes in neural function may precede atrophy in FTD.

1.10 References

Adolphs R. Fear, faces, and the human amygdala. Curr Opin Neurobiol 2008; 18: 166-72.

Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR. A mechanism for impaired fear recognition after amygdala damage. Nature 2005; 433: 68-72.

Adolphs R, Tranel D, Hamann S, Young AW, Calder AJ, Phelps EA, et al. Recognition of facial emotion in nine individuals with bilateral amygdala damage. Neuropsychologia 1999; 37: 1111-7.

Alzheimer A. Über eigenartige Krankheitsfalle des späteren Alters. Z Gesamte Neurol Psychiatr 1911; 4: 356-385.

Amaral D, Price J, Pitkanen A, Carmichael S. Anatomical organization of the primate amygdaloid complex. In the amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction. In: J. Aggleton ed. New York: Wiley-Liss, 1992: 1-66.

Amting JM, Greening SG, Mitchell DG. Multiple mechanisms of consciousness: the neural correlates of emotional awareness. J Neurosci 2010; 30: 10039-47.

Arvanitakis Z. Update on frontotemporal dementia. Neurologist 2010; 16: 16-22.

Blair R, Mitchell D, Peschardt K, Colledge E, Leonard R, Shine J, et al. Reduced sensitivity to others' fearful expressions in psychopathic individuals. Personality and individual differences 2004; 37: 1111-1122.

Blair RJ. A cognitive developmental approach to mortality: investigating the psychopath. Cognition 1995; 57: 1-29.

Blair RJ. Facial expressions, their communicatory functions and neuro-cognitive substrates. Philos Trans R Soc Lond B Biol Sci 2003; 358: 561-72.

Blair RJ, Cipolotti L. Impaired social response reversal. A case of 'acquired sociopathy'. Brain 2000; 123 (Pt 6): 1122-41.

Blair RJ, Jones L, Clark F, Smith M. The psychopathic individual: a lack of responsiveness to distress cues? Psychophysiology 1997; 34: 192-8.

Blair RJ, Morris JS, Frith CD, Perrett DI, Dolan RJ. Dissociable neural responses to facial expressions of sadness and anger. Brain 1999; 122 (Pt 5): 883-93.

Boccardi M, Sabattoli F, Laakso MP, Testa C, Rossi R, Beltramello A, et al. Frontotemporal dementia as a neural system disease. Neurobiol Aging 2005; 26: 37-44.

Calder AJ, Beaver JD, Davis MH, van Ditzhuijzen J, Keane J, Lawrence AD. Disgust sensitivity predicts the insula and pallidal response to pictures of disgusting foods. Eur J Neurosci 2007; 25: 3422-8.

Corden B, Critchley HD, Skuse D, Dolan RJ. Fear recognition ability predicts differences in social cognitive and neural functioning in men. J Cogn Neurosci 2006; 18: 889-97.

Darwin C. The expression of the emotions in man and animals. London: Albemarle, 1872.

Davatzikos C, Resnick SM, Wu X, Parmpi P, Clark CM. Individual patient diagnosis of AD and FTD via high-dimensional pattern classification of MRI. Neuroimage 2008; 41: 1220-7.

de Araujo IE, Rolls ET, Kringelbach ML, McGlone F, Phillips N. Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. Eur J Neurosci 2003; 18: 2059-68.

Decety J, Jackson PL. The functional architecture of human empathy. Behav Cogn Neurosci Rev 2004; 3: 71-100.

Diehl-Schmid J, Grimmer T, Drzezga A, Bornschein S, Riemenschneider M, Forstl H, et al. Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study. Neurobiol Aging 2007a; 28: 42-50.

Diehl-Schmid J, Pohl C, Ruprecht C, Wagenpfeil S, Foerstl H, Kurz A. The Ekman 60 Faces Test as a diagnostic instrument in frontotemporal dementia. Arch Clin Neuropsychol 2007b; 22: 459-64.

Dolcos F, LaBar KS, Cabeza R. Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. Neuroimage 2004; 23: 64-74.

Eslinger PJ, Moore P, Anderson C, Grossman M. Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. J Neuropsychiatry Clin Neurosci 2011; 23: 74-82.

Eslinger PJ, Moore P, Troiani V, Antani S, Cross K, Kwok S, et al. Oops! Resolving social dilemmas in frontotemporal dementia. J Neurol Neurosurg Psychiatry 2007; 78: 457-60.

Fernandez-Duque D, Black SE. Impaired recognition of negative facial emotions in patients with frontotemporal dementia. Neuropsychologia 2005; 43: 1673-87.

Finch N, Baker M, Crook R, Swanson K, Kuntz K, Surtees R, et al. Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. Brain 2009; 132: 583-91.

Finger EC, Marsh AA, Kamel N, Mitchell DG, Blair JR. Caught in the act: the impact of audience on the neural response to morally and socially inappropriate behavior. Neuroimage 2006; 33: 414-21.

Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain 2007; 130: 2616-35.

Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, et al. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 2009; 34: 418-32.

Gamer M, Buchel C. Amygdala activation predicts gaze toward fearful eyes. J Neurosci 2009; 29: 9123-6.

Garcin B, Lillo P, Hornberger M, Piguet O, Dawson K, Nestor PJ, et al. Determinants of survival in behavioral variant frontotemporal dementia. Neurology 2009; 73: 1656-61.

Gottfried JA, O'Doherty J, Dolan RJ. Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. J Neurosci 2002; 22: 10829-37.

Graff-Radford NR, Woodruff BK. Frontotemporal dementia. Semin Neurol 2007; 27: 48-57.

Harmer CJ, Thilo KV, Rothwell JC, Goodwin GM. Transcranial magnetic stimulation of medial-frontal cortex impairs the processing of angry facial expressions. Nat Neurosci 2001; 4: 17-8.

Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain 1992; 115 (Pt 6): 1783-806.

Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002; 73: 371-6.

Jabbi M, Swart M, Keysers C. Empathy for positive and negative emotions in the gustatory cortex. Neuroimage 2007; 34: 1744-53.

Jeong Y, Cho SS, Park JM, Kang SJ, Lee JS, Kang E, et al. 18F-FDG PET findings in frontotemporal dementia: an SPM analysis of 29 patients. J Nucl Med 2005; 46: 233-9.

Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 1997; 17: 4302-11.

Keane J, Calder AJ, Hodges JR, Young AW. Face and emotion processing in frontal variant frontotemporal dementia. Neuropsychologia 2002; 40: 655-65.

Kertesz A. Frontotemporal dementia: a topical review. Cogn Behav Neurol 2008; 21: 127-33.

Kertesz A, Blair M, McMonagle P, Munoz DG. The diagnosis and course of frontotemporal dementia. Alzheimer Dis Assoc Disord 2007; 21: 155-63.

Kertesz A, Jesso S, Harciarek M, Blair M, McMonagle P. What is semantic dementia?: a cohort study of diagnostic features and clinical boundaries. Arch Neurol 2010; 67: 483-9.

Kertesz A, Nadkarni N, Davidson W, Thomas AW. The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. J Int Neuropsychol Soc 2000; 6: 460-8.

Kipps CM, Duggins AJ, McCusker EA, Calder AJ. Disgust and happiness recognition correlate with anteroventral insula and amygdala volume respectively in preclinical Huntington's disease. J Cogn Neurosci 2007; 19: 1206-17.

Kipps CM, Hodges JR. Theory of mind in frontotemporal dementia. Soc Neurosci 2006; 1: 235-44.

Lavenu I, Pasquier F, Lebert F, Petit H, Van der Linden M. Perception of emotion in frontotemporal dementia and Alzheimer disease. Alzheimer Dis Assoc Disord 1999; 13: 96-101.

LeDoux J. The emotional brain; the mysterious underpinning of emotional life. New York: Weidenfeld & Nicolson, 1998.

Levesque J, Eugene F, Joanette Y, Paquette V, Mensour B, Beaudoin G, et al. Neural circuitry underlying voluntary suppression of sadness. Biol Psychiatry 2003; 53: 502-10.

Lough S, Kipps CM, Treise C, Watson P, Blair JR, Hodges JR. Social reasoning, emotion and empathy in frontotemporal dementia. Neuropsychologia 2006; 44: 950-8.

Lund-Manchester. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry 1994; 57: 416-8.

Marsh AA, Blair KS, Jones MM, Soliman N, Blair RJ. Dominance and submission: the ventrolateral prefrontal cortex and responses to status cues. J Cogn Neurosci 2009; 21: 713-24.

Marsh AA, Blair RJ. Deficits in facial affect recognition among antisocial populations: a meta-analysis. Neurosci Biobehav Rev 2008; 32: 454-65.

Marsh AA, Kozak MN, Ambady N. Accurate identification of fear facial expressions predicts prosocial behavior. Emotion 2007; 7: 239-51.

Massimo L, Powers C, Moore P, Vesely L, Avants B, Gee J, et al. Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. Dement Geriatr Cogn Disord 2009; 27: 96-104.

McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001; 58: 1803-9.

McMurtray AM, Chen AK, Shapira JS, Chow TW, Mishkin F, Miller BL, et al. Variations in regional SPECT hypoperfusion and clinical features in frontotemporal dementia. Neurology 2006; 66: 517-22.

McNeill R, Sare GM, Manoharan M, Testa HJ, Mann DM, Neary D, et al. Accuracy of single-photon emission computed tomography in differentiating frontotemporal dementia from Alzheimer's disease. J Neurol Neurosurg Psychiatry 2007; 78: 350-5.

Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. J Neurol Neurosurg Psychiatry 2006; 77: 4-7.

Miller BL, Darby A, Benson DF, Cummings JL, Miller MH. Aggressive, socially disruptive and antisocial behaviour associated with fronto-temporal dementia. Br J Psychiatry 1997; 170: 150-4.

Mitchell DG. The nexus between decision making and emotion regulation: a review of convergent neurocognitive substrates. Behav Brain Res 2011; 217: 215-31.

Morris JS, deBonis M, Dolan RJ. Human amygdala responses to fearful eyes. Neuroimage 2002; 17: 214-22.

Morris JS, Friston KJ, Buchel C, Frith CD, Young AW, Calder AJ, et al. A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain 1998; 121 (Pt 1): 47-57.

Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, et al. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 1996; 383: 812-5.

Neary D, Snowden J, Mann D. Frontotemporal dementia. Lancet Neurol 2005; 4: 771-80.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546-54.

O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F. Representation of pleasant and aversive taste in the human brain. J Neurophysiol 2001; 85: 1315-21.

Omar R, Rohrer JD, Hailstone JC, Warren JD. Structural neuroanatomy of face processing in frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry 2010.

Pereira JM, Williams GB, Acosta-Cabronero J, Pengas G, Spillantini MG, Xuereb JH, et al. Atrophy patterns in histologic vs clinical groupings of frontotemporal lobar degeneration. Neurology 2009; 72: 1653-60.

Perry RJ, Miller BL. Behavior and treatment in frontotemporal dementia. Neurology 2001; 56: S46-51.

Pessoa L, McKenna M, Gutierrez E, Ungerleider LG. Neural processing of emotional faces requires attention. Proc Natl Acad Sci U S A 2002; 99: 11458-63.

Pessoa L, Ungerleider LG. Neuroimaging studies of attention and the processing of emotion-laden stimuli. Prog Brain Res 2004; 144: 171-82.

Phillips ML, Young AW, Scott SK, Calder AJ, Andrew C, Giampietro V, et al. Neural responses to facial and vocal expressions of fear and disgust. Proc Biol Sci 1998; 265: 1809-17.

Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, et al. A specific neural substrate for perceiving facial expressions of disgust. Nature 1997; 389: 495-8.

Pick A. Über die Beziehungen der senilen Hirnatrophie zur Aphasie. Prag Med Wochenschr 1892; 17: 165-167.

Rabinovici GD, Seeley WW, Kim EJ, Gorno-Tempini ML, Rascovsky K, Pagliaro TA, et al. Distinct MRI atrophy patterns in autopsy-proven Alzheimer's disease and frontotemporal lobar degeneration. Am J Alzheimers Dis Other Demen 2007; 22: 474-88.

Rahman S, Sahakian BJ, Hodges JR, Rogers RD, Robbins TW. Specific cognitive deficits in mild frontal variant frontotemporal dementia. Brain 1999; 122 (Pt 8): 1469-93.

Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, et al. Structural anatomy of empathy in neurodegenerative disease. Brain 2006; 129: 2945-56.

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, van Swieten JC, et al. Sensitivity of consensus diagnostic criteria in autopsy confirmed patients with behavioral variant frontotemporal dementia (bvFTD): First report of the international bvFTD Criteria Consortium (FTDC). Dement Geriatr Cogn Disord 2010; 30.

Rohrer J, Ahsan R, Isaacs A, Nielsen J, Ostergaard L, Scahill R, et al. Presymptomatic generalized brain atrophy in frontotemporal dementia caused by CHMP2B mutation. Dementia and geriatric cognitive disorders 2009a; 27: 182-186.

Rohrer J, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology 2009b; 73: 1451-1456.

Rombouts SA, van Swieten JC, Pijnenburg YA, Goekoop R, Barkhof F, Scheltens P. Loss of frontal fMRI activation in early frontotemporal dementia compared to early AD. Neurology 2003; 60: 1904-8.

Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 2002a; 58: 198-208.

Rosen HJ, Pace-Savitsky K, Perry RJ, Kramer JH, Miller BL, Levenson RW. Recognition of emotion in the frontal and temporal variants of frontotemporal dementia. Dement Geriatr Cogn Disord 2004; 17: 277-81.

Rosen HJ, Perry RJ, Murphy J, Kramer JH, Mychack P, Schuff N, et al. Emotion comprehension in the temporal variant of frontotemporal dementia. Brain 2002b; 125: 2286-95.

Rosen HJ, Wilson MR, Schauer GF, Allison S, Gorno-Tempini ML, Pace-Savitsky C, et al. Neuroanatomical correlates of impaired recognition of emotion in dementia. Neuropsychologia 2006; 44: 365-73.

Rosso SM, Donker Kaat L, Baks T, Joosse M, de Koning I, Pijnenburg Y, et al. Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. Brain 2003; 126: 2016-22.

Russell JA. Is there universal recognition of emotion from facial expression? A review of the cross-cultural studies. Psychol Bull 1994; 115: 102-41.

Salmon E, Garraux G, Delbeuck X, Collette F, Kalbe E, Zuendorf G, et al. Predominant ventromedial frontopolar metabolic impairment in frontotemporal dementia. Neuroimage 2003; 20: 435-40.

Seeley WW. Anterior insula degeneration in frontotemporal dementia. Brain Struct Funct 2010; 214: 465-75.

Seeley WW, Allman JM, Carlin DA, Crawford RK, Macedo MN, Greicius MD, et al. Divergent social functioning in behavioral variant frontotemporal dementia and Alzheimer disease: reciprocal networks and neuronal evolution. Alzheimer Dis Assoc Disord 2007; 21: S50-7.

Seeley WW, Bauer AM, Miller BL, Gorno-Tempini ML, Kramer JH, Weiner M, et al. The natural history of temporal variant frontotemporal dementia. Neurology 2005; 64: 1384-90.

Seeley WW, Crawford R, Rascovsky K, Kramer JH, Weiner M, Miller BL, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Arch Neurol 2008; 65: 249-55.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. Neuron 2009; 62: 42-52.

Short RA, Broderick DF, Patton A, Arvanitakis Z, Graff-Radford NR. Different patterns of magnetic resonance imaging atrophy for frontotemporal lobar degeneration syndromes. Arch Neurol 2005; 62: 1106-10.

Snowden J, Goulding P, Neary D. Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 1989; 2: 167-182.

Snowden J, Neary D, Mann D. Fronto-temporal lobar degeneration: Fronto-temporal dementia, progressive aphasia, semantic dementia. Edinburgh: Churchill Livingstone, 1996.

Snowden J, Neary D, Mann D. Frontotemporal lobar degeneration: clinical and pathological relationships. Acta Neuropathol 2007; 114: 31-8.

Snowden JS, Neary D, Mann DM, Goulding PJ, Testa HJ. Progressive language disorder due to lobar atrophy. Ann Neurol 1992; 31: 174-83.

Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H. Neural structures associated with recognition of facial expressions of basic emotions. Proc Biol Sci 1998; 265: 1927-31.

Surguladze SA, Brammer MJ, Young AW, Andrew C, Travis MJ, Williams SC, et al. A preferential increase in the extrastriate response to signals of danger. Neuroimage 2003; 19: 1317-28.

Talbot PR, Lloyd JJ, Snowden JS, Neary D, Testa HJ. A clinical role for 99mTc-HMPAO SPECT in the investigation of dementia? J Neurol Neurosurg Psychiatry 1998; 64: 306-13.

van der Flier W, Pijnenburg Y, Fox N, Scheltens P. Early-onset versus late-onset Alzheimer's disease: the case of the missing APOE ε4 allele. Lancet Neurol 2011; 10: 280-288.

Varma AR, Adams W, Lloyd JJ, Carson KJ, Snowden JS, Testa HJ, et al. Diagnostic patterns of regional atrophy on MRI and regional cerebral blood flow change on SPECT in young onset patients with Alzheimer's disease, frontotemporal dementia and vascular dementia. Acta Neurol Scand 2002; 105: 261-9.

Vuilleumier P, Armony JL, Driver J, Dolan RJ. Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron 2001; 30: 829-41.

Vuilleumier P, Armony JL, Driver J, Dolan RJ. Distinct spatial frequency sensitivities for processing faces and emotional expressions. Nat Neurosci 2003; 6: 624-31.

Vuilleumier P, Richardson MP, Armony JL, Driver J, Dolan RJ. Distant influences of amygdala lesion on visual cortical activation during emotional face processing. Nat Neurosci 2004; 7: 1271-8.

Warrington EK. The selective impairment of semantic memory. Q J Exp Psychol 1975; 27: 635-57.

Whitwell JL, Przybelski SA, Weigand SD, Ivnik RJ, Vemuri P, Gunter JL, et al. Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. Brain 2009; 132: 2932-46.

Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD, et al. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. Brain 2010; 133: 1352-67.

CHAPTER 2

Elucidating the Functional Neural Correlates of Emotional Face Processing Deficits in Behavioural Variant Frontotemporal Dementia

2.1 Introduction

Frontotemporal dementia (FTD) is a neurodegenerative disorder characterized by progressive dysfunction in social behaviour typically beginning in mid-life (50s-60s). FTD is associated with abnormal accumulation of neuronal proteins and neuronal loss, which likely begins decades before the first manifestation of clinical symptoms (Finch et al., 2009; Rohrer et al., 2009). This leads to selective, but progressive, loss of brain function and tissue in regions of the frontal and/or temporal lobes. The core clinical diagnostic features of behavioural variant FTD (bvFTD), the most common clinical subtype of frontotemporal lobar degeneration, include an insidious onset and gradual disease progression, early deficits in interpersonal conduct, early behavioural dysregulation, apathy, and loss of insight (Lund-Manchester, 1994; McKhann et al., 2001; Neary et al., 1998). Similar behavioural and emotional symptoms frequently co-occur in FTD patients who show semantic deficits (Hodges et al., 1992; Kertesz et al., 2007; Rosen et al., 2002a; Snowden et al., 1992). One of the hallmark symptoms of bvFTD, irrespective of semantic impairment, is a loss of empathy for others. This symptom is thought to be partially accounted for by a reduction in human emotion recognition (Diehl-Schmid et al., 2007; Lough et al., 2006; Rankin et al., 2005). While a growing body of research has associated regions of atrophy with bvFTD clinical symptoms (Eslinger et al., 2011; Huey et al., 2009; Massimo et al., 2009; Woolley et al., 2007), the functional neural correlates of the core emotion processing deficits in bvFTD have yet to be examined.

Facial expressions are one way in which we communicate emotional information critical for successful social behaviour (Blair, 2003; Darwin, 1872). Deficient facial

expression recognition, particularly recognition of negative expressions such as fear and anger, is associated with inappropriate social behaviours (Blair and Cipolotti, 2000; Blair et al., 2004; Corden et al., 2006; Marsh and Blair, 2008). Previous studies have demonstrated that patients with bvFTD show deficits in facial expression recognition, while general face processing abilities such as facial identity discrimination (Rosen et al., 2002b, 2004), facial familiarity judgment (Keane et al., 2002), and gender discrimination (Fernandez-Duque and Black, 2005) are comparatively preserved. Patients with mild bvFTD show impaired positive and negative facial emotion processing relative to healthy controls (Diehl-Schmid et al., 2007), and impaired negative expression recognition relative to patients with mild Alzheimer's disease (Fernandez-Duque and Black, 2005; Lavenu et al., 1999). Abnormalities in the recognition of negative emotional expressions have been noted both in patients with bvFTD with frontal-dominant (Keane et al., 2002; Lough et al., 2006) and temporal-dominant atrophy (Rosen et al., 2002b). However, evidence exists that emotional social-cognitive deficits may be more pronounced in the frontal subtype. Direct comparison of bvFTD patients with frontal versus temporal predominant atrophy demonstrates that while both groups were impaired on negative emotions, frontal-dominant type patients showed additional deficits recognizing happy facial expressions (Rosen et al., 2004).

The neural regions supporting facial expression processing in healthy adults show great overlap with the neural regions affected early in the course of bvFTD. In the early stages of bvFTD, atrophy is predominant in a frontal paralimbic network, including the anterior cingulate cortex, anterior insula, frontal pole, amygdala, and striatum, with frequent right hemisphere predominance (Rosen et al., 2002a; Seeley et al., 2008). In

patients who develop semantic deficits in addition to behavioural and personality symptoms, atrophy is commonly observed bilaterally in the temporal poles, amygdala, ventromedial prefrontal cortex, insula, and inferoposterior temporal regions (Rosen et al., 2002a; Seeley et al., 2005). A number of lesion and functional neuroimaging studies have delineated the neural regions associated with healthy facial expression processing. Regions of the temporal-occipital cortex, namely the fusiform gyrus, are robustly activated when viewing faces and processing basic facial features (Haxby et al., 2000; Kanwisher et al., 1997; Winston et al., 2004). Activity in this region is augmented for emotional relative to neutral expressions (Fusar-Poli et al., 2009; Morris et al., 1998; Vuilleumier et al., 2001). Emotional faces also activate frontotemporal limbic regions, with some unique emotion-specific patterns. The amygdala is typically active when fearful, sad or happy faces are viewed (Adolphs et al., 1994; Fusar-Poli et al., 2009; Pessoa et al., 2002; Whalen et al., 1998). Rostral anterior cingulate/ventromedial prefrontal cortex activity is greatest during happy and fearful faces (Fusar-Poli et al., 2009). In contrast, the anterior insula and ventrolateral prefrontal cortex are activated by disgusted and angry facial expressions, respectively (Blair et al., 1999; Fusar-Poli et al., 2009; Phillips et al., 1997).

Despite the body of data supporting facial expression recognition deficits in bvFTD, the functional neuroanatomy of facial expression processing has yet to be examined and delineated in this disease. Functional magnetic resonance imaging (fMRI) combined with targeted cognitive tasks offers a potentially powerful technique to detect neural dysfunction directly related to symptomatology associated with a neurodegenerative disease *prior* to detectable atrophy (Dickerson et al., 2005). In the

present study we used fMRI while correcting for voxel-wise atrophy across the brain to index the functional brain activity during implicit emotional facial expression processing in bvFTD patients and matched controls. We hypothesized that patients with bvFTD would show decreased blood-oxygen-level dependent (BOLD) signal, following measurable atrophy correction, in frontotemporal regions that are both directly affected by bvFTD pathology and critical for facial expression processing. Specifically, we predicted that bvFTD patients would show reduced BOLD signal compared to controls in ventrolateral prefrontal cortex (inferior frontal gyrus) and anterior insula while viewing angry expressions, in the amygdala during fearful expressions, and in the insula during disgusted expressions. Second, we predicted that direct comparisons between bvFTD patients without semantic dementia symptoms and those with semantic dementia symptoms would reveal functional group differences, showing reduced frontal activation during angry, fearful, happy, and sad expressions in bvFTD patients without semantic deficits and reduced activation in anterior temporal regions such as the amygdala during fearful, happy, and sad expressions in patients with semantic impairments. Third, due to functional abnormalities in limbic regions, we predicted that bvFTD patients would show indirect reductions in BOLD signal in posterior downstream targets of the limbic system that are typically unaffected in bvFTD, but perform a more general role in face processing, such as fusiform cortex. We predicted that functional abnormalities following all group contrasts would be present even after a whole brain voxel-wise grey matter correction for atrophy/volume differences, thus representing a critical target in the development of tools for early diagnosis and treatment.

2.2 Methods

2.2.1 Participants

Following a complete description of the study, all participants (or their surrogates) provided written informed consent. The procedures were approved by the Health Sciences Research Ethics Board at the University of Western Ontario. Patients were recruited through the Cognitive Neurology and Alzheimer Research Centre (CNARC) at St. Joseph's Hospital in London, Ontario, Canada. Healthy controls were recruited through the local FTD caregiver support group and the CNARC volunteer pool. Patients included in the study met Neary Criteria for bvFTD (Neary et al., 1998) and had supportive neuroimaging (MRI, CT, or SPECT; see Figure 2.1 for MRI pictures of example bvFTD patients included in the study). Study exclusion criteria included any history of traumatic brain injury or other neurological or psychiatric disorder apart from bvFTD. In total, 24 bvFTD patients and 18 healthy controls were initially enrolled. Twenty patients with bvFTD successfully completed the fMRI scan. Four patients were unable to complete the fMRI scan (secondary to claustrophobia or excessive movement). BvFTD patients were further subcategorized according to the presence (n = 8) or absence (n = 12) of semantic dementia symptoms (Hodges et al., 1992; Snowden et al., 1989; Warrington, 1975), and were matched as closely as possible to healthy controls in age, gender, handedness, and education (Table 2.1; see Appendix A for subjects' medical history).

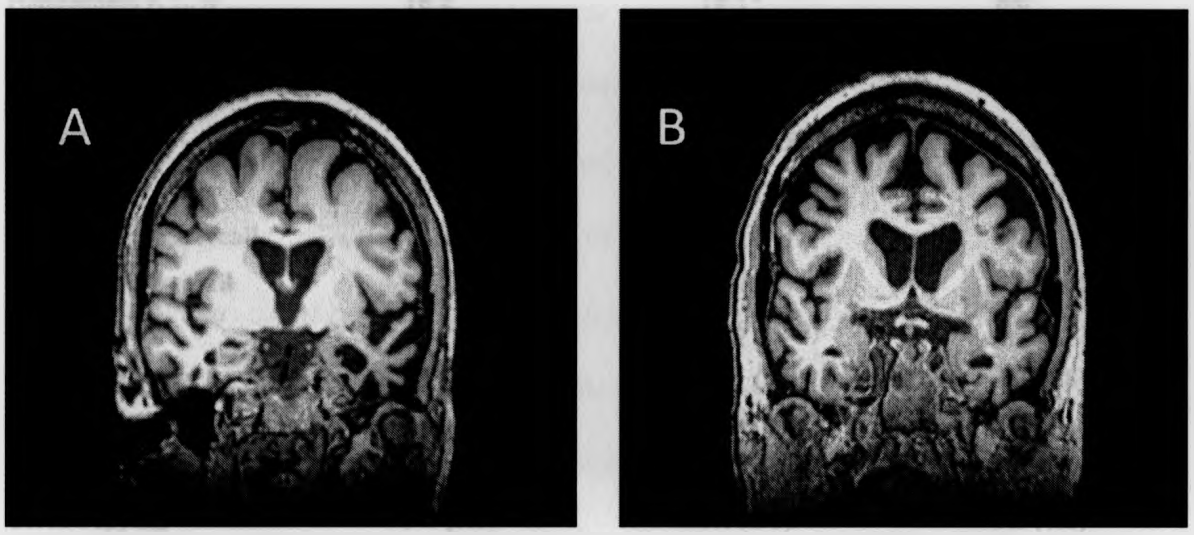

Figure 2.1. MRI pictures of bvFTD patients included in the present study (left side = right hemisphere; coronal slices). (A) 71 year old female bvFTD patient with semantic deficits, approximately 4.5 years post symptoms onset, demonstrating predominantly temporal lobe atrophy, left greater than right. (B) 61 year old male bvFTD patient without semantic deficits, approximately 7 years post symptoms onset, demonstrating predominantly frontal lobe atrophy.

Table 2.1. Subject demographic and neuropsychological characteristics

	Healthy controls	bvFTD without SD	bvFTD with SD
Age, years	62.4 (10.8)	62.8 (9.2)	69.1 (3.8)
M:F, *n*	13:5	10:2	5:3
Handedness R:L, *n*	16:2	10:1*	8:0
Education, years	15.8 (5.0)**	11.3 (3.2)	11.4 (2.9)
Illness duration, years	NA	5.3 (4.0)	5.5 (2.2)
MMSE	28.7 (1.8)	22.5 (6.5)	17.4 (6.9)
FBI	NA	34.0 (11.9)	39.6 (8.8)
Immediate prose recall	10.8 (3.2)	4.3 (4.1)	1.3 (1.6)
Delayed prose recall	9.7 (3.8)	3.2 (3.7)	0.6 (1.0)
Letter fluency	36.7 (11.7)	19.6 (12.9)	9.4 (6.9)
Semantic fluency	17.8 (4.4)	11.1 (5.9)	4.2 (5.8)
Object naming	20.0 (0.0)	18.0 (3.4)	12.0 (4.6)
Spontaneous clock drawing	9.13 (0.7)	7.9 (2.6)	7.7 (2.5)
Clock copying	9.7 (0.5)	8.0 (2.6)	9.0 (0.0)
Beck Depression Inventory	6.8 (4.3)	10.2 (8.2)	NA
Trails A	38.6 (11.1)	42.7 (15.4)	78.6 (37.1)
Trails B	102.5 (55.0)	88.0 (38.0)	91.0 (NA)
ANART	13.4 (8.9)	30.6 (8.8)	38.5 (6.6)
WCST	5.5 (0.9)	2.6 (2.2)	3.5 (2.4)
Stroop A	91.5 (16.0)	61.5 (27.4)	38.7 (24.1)
Stroop B	63.4 (14.0)	39.1 (24.8)	25.5 (29.0)
Stroop C	35.0 (7.6)	19.5 (16.3)	8.0 (9.9)

Values represent mean (standard deviation). Not all patients completed all neuropsychological tests. SD = semantic deficits. * One bvFTD without semantic deficits patient was ambidextrous. ** Healthy controls > bvFTD without SD = bvFTD with SD, $p < .05$. See Appendix B for neuropsychological tests sample sizes and Appendix C for descriptions of neuropsychological tests.

2.2.2 fMRI task

Participants were presented with photographs of angry, disgusted, fearful, happy, and sad emotional facial expressions from the Karolinska Directed Emotional Faces, a cross-culturally validated stimulus set (Lundqvist et al., 1998). The facial stimuli were cropped to remove hair and neck regions, eliminating extraneous features. Emotional expressions were morphed with neutral facial expressions from the same actors using Abrosoft FantaMorph (Abrosoft, Beijing, Version 4) software to create two levels of emotional intensity (40% and 100% intensity). A total of 160 different faces were available for random selection for each run of the paradigm. The stimuli were projected onto a screen that could be viewed by the subject via a positioned mirror above the MRI scanner head-coil. Following previous studies (Blair et al., 1999; Marsh et al., 2008; Phillips et al., 1998), participants were required to indicate the gender of the faces by making a button press response while viewing the faces in the scanner. Stimuli were presented in a rapid event-related manner using E-prime software (Schneider et al., 2002). Subjects completed 3 independent runs of the task. Each run was composed of 104 randomly occurring trials: 80 emotional faces presented for 2.5 seconds followed by a fixation cross for 0.5 seconds, and 24 interspersed "jittered" trials consisting of a fixation cross presented for 3 seconds (Figure 2.2). Each run lasted 5 minutes and 42 seconds. Practice trials outside of the scanner were carried out for both participant groups to ensure task instructions.

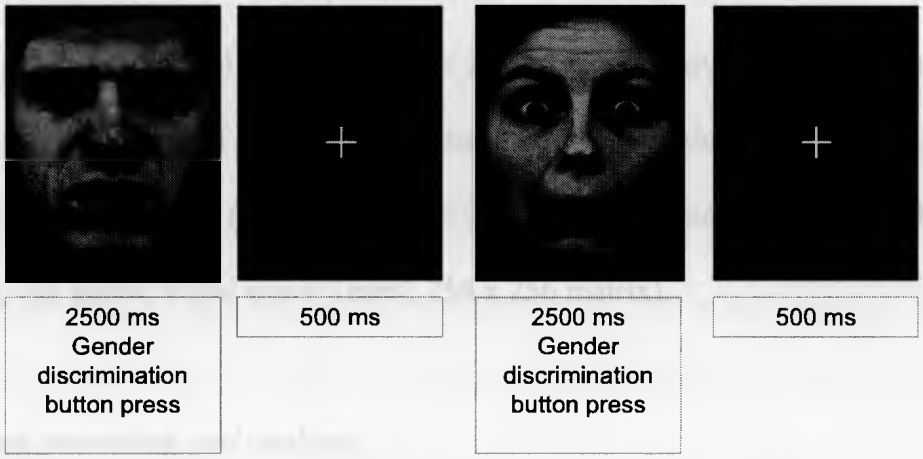

Figure 2.2. Trial schematic depicting the time-course for two consecutive trials. The first face shows a disgusted male at 40% emotional intensity and the second face shows a 100% fearful female.

2.2.3 Image acquisition

Data was acquired using a 3-Tesla Siemens Tim Trio MRI scanner with a 32 channel head-coil. Functional data was acquired using T_2*-gradient echo-planar imaging sequence (45 contiguous slices of 2 x 2mm in plane; slice thickness = 2.5mm; repetition time = 3000ms; echo time = 30ms; field of view = 24cm; 120 x 120 matrix). This sequence generated a voxel resolution of 2 x 2 x 2.5mm. Following the final task run, a high resolution structural T_1-weighted acquisition of the complete brain volume was obtained in the axial plane (repetition time = 2300ms; echo time = 4.25ms; field of view = 25.6cm; 192 slices; voxel size = $1mm^3$; 256 x 256 matrix).

2.2.4 Image processing and analysis:

2.2.4.1 Structural imaging

To account for grey matter volume differences influencing the fMRI signal, volumetric brain analysis was carried out. Atrophy and volume differences were corrected for by including a covariate into the fMRI analysis reflecting subjects' voxel-wise grey matter tissue probabilities. T_1-weighted MRI images were analyzed using FSL tools (Smith et al., 2004; www.fmrib.ox.ac.uk/fsl). Initially, structural images were brain-extracted using BET (Smith, 2002). Second, tissue was segmented into GM, WM, and CSF using FAST4 (Zhang et al., 2001). The resulting grey matter volume images were aligned to the MNI152 template using the affine registration tool FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001), and smoothed with an isotropic Gaussian kernel with a sigma of 4mm (~9mm FWHM). Prior to fMRI analysis, grey matter probability maps were realigned to Talaraich standard space.

2.2.4.2 Functional imaging

The fMRI data were preprocessed and analyzed using Analysis of Functional Neuroimages (AFNI; Cox, 1996) software package. The first five volumes of each run were discarded to ensure magnetization equilibrium. Motion correction was accomplished by registering all BOLD data of each run to the last volume of the last run, immediately preceding the anatomical scan. Subjects' functional data were spatially smoothed with a 4mm isotropic Gaussian kernel (~9mm FWHM). The time series data were normalized by dividing the signal intensity of a voxel at each time point by the mean signal intensity of that voxel for each run and multiplying the result by 100. Resultant regression coefficients represented the percent signal change relative to the mean. Regressors were created to represent trials when a response was made for each emotion/intensity by convolving the stimulus events with a gamma-variate basis function to account for the slow hemodynamic response. A baseline plus linear drift and quadratic trend were modeled to the time series of each voxel to correct for voxel-wise correlated drifting, producing a beta coefficient and *t*-statistic for each voxel and regressor. Subjects' anatomical scans were registered to Talaraich standard space, allowing each subject's functional data to be aligned to their own normalized anatomical template for group analysis.

Subjects' regressors for 40% and 100% emotional intensity were initially averaged within emotions [e.g. (Angry-40% + Angry-100%)/2] to increase statistical power. Planned voxel-wise *t*-tests, covaried for voxel-wise grey matter, were performed to determine whether emotion-specific group differences in BOLD activation persisted

when correlations between grey matter volume and activation were controlled for. To elucidate changes in activation patterns in response to emotional faces, the following two comparisons were examined: all bvFTD patients versus healthy controls, and bvFTD patients without semantic deficits versus bvFTD patients with semantic deficits. Whole brain contrasts were thresholded at $p<0.005$ and corrected for multiple comparisons to $p<0.05$ using AFNI's 3dClustSim spatial clustering program with 10, 000 Monte Carlo simulations on a whole brain EPI matrix. This operation estimates the probability of random noise producing a cluster of a given size, based on a specified uncorrected voxel-wise threshold. The above whole brain contrast yielded significant corrected clusters with a minimum volume of $270mm^3$. The one exception was the amygdala, which was thresholded at $p<0.05$ (small-volume corrected with a significant cluster at a minimum volume of $430mm^3$), because of *a priori* predictions concerning this structure's involvement in face processing.

2.3 Results

2.3.1 Behavioural data

All subjects made successful gender discriminations for the majority of trials (Table 2.2). Healthy controls performed the gender discrimination at higher accuracy than bvFTD patients ($df = 36$, $p<0.05$ for between group emotion contrasts). It was observed that bvFTD patients were often inconsistent with the response buttons used for male versus female. Thus, we evaluated gender discrimination data that was available on 12 of the 20 bvFTD patients from an independent study using the same facial stimuli, where patients verbally indicated the gender. When responses were reported verbally,

performance improved ($M = 88.54\%$, $SD = 9.82\%$) relative to the button press gender discrimination task in the present study. Although bvFTD patients responded to significantly less trials than controls (Table 2.2), patients' overall response frequency remained high ($M = 85.2\%$, $SD = 15.0\%$).

Table 2.2. Comparison between bvFTD patients and healthy controls on gender discrimination accuracy and response frequency

	Healthy controls	bvFTD
Gender discrimination accuracy[†,*]		
Angry	91.1 (6.4)	75.7 (18.0)
Disgust	93.4 (5.4)	77.3 (19.9)
Fear	93.2 (3.7)	76.7 (20.7)
Happy	92.0 (2.6)	76.2 (21.9)
Sad	93.7 (3.8)	77.1 (20.9)
Response frequency		
Angry	97.9 (2.7)	85.0 (14.9)
Disgust	98.4 (2.4)	84.4 (16.1)
Fear	99.2 (1.5)	84.8 (16.5)
Happy	98.5 (2.0)	87.0 (14.8)
Sad	98.3 (2.9)	84.7 (15.1)

Values represent mean percentage (standard deviation). [†]Only responsive trials included in calculations. [*]bvFTD percent correct > 50%, $p<0.05$ for all emotions.

2.3.2 Imaging data

2.3.2.1 BvFTD patients versus healthy controls (Table 2.3)

Anger

As predicted, relative to healthy controls, bvFTD patients showed reduced activity in the right inferior frontal gyrus (BA 47; $t(36) = -3.78$, $p<0.005$) while viewing angry expressions (Figure 2.3A). BvFTD patients also demonstrated decreased BOLD signal in the left amygdala ($t(36) = -2.11$, $p<0.05$). Consistent with predictions that secondary reductions would be observed in temporal-occipital visual areas in bvFTD, reduced BOLD signal was observed in the left fusiform gyrus (BA 37; $t(36) = -3.18$, $p<0.005$) (Figure 2.3B) and right cuneus (BA 17; $t(36) = -3.43$, $p<0.005$) compared to controls. In contrast, increased BOLD signal was observed in bvFTD patients compared to controls in the right inferior parietal lobule (BA 39; $t(36) = 3.66$, $p<0.005$) and left posterior cingulate cortex (BA 31; $t(36) = 3.12$, $p<0.005$) (Figure 2.3C).

Disgust

Consistent with the role of the insula in the processing of disgusted stimuli and the involvement of this region early in the course of bvFTD, patients with bvFTD demonstrated decreased BOLD signal in the right (BA 13; $t(36) = -3.21$, $p<0.005$) and left insula (BA 13; $t(36) = -3.49$, $p<0.005$) to disgusted facial expressions (Figure 2.4). As well, patients showed reduced activation in the left lingual gyrus (extending into fusiform cortex; BA 18; $t(36) = -3.41$, $p<0.005$) and right middle occipital gyrus (BA 18; $t(36) = -3.12$, $p<0.005$) compared to control participants.

Happy

Relative to healthy controls, bvFTD patients demonstrated decreased BOLD signal in the left amygdala ($t(36) = -2.31, p<0.05$) (Figure 2.5), yet increased BOLD signal in the right inferior parietal lobule (BA 39; $t(36) = 3.05, p<0.005$).

Fear

BvFTD patients demonstrated decreased BOLD signal relative to controls in the left medial frontal gyrus (BA 6; $t(36) = -3.25, p<0.005$), left lingual gyrus (extending into fusiform cortex; BA 18; $t(36) = -3.60, p<0.005$), left middle occipital gyrus (BA 18; $t(36) = -3.23, p<0.005$), and right cuneus (BA 17; $t(36) = -3.25, p<0.005$ while viewing fearful expressions.

Sad

Compared to healthy controls, bvFTD patients demonstrated decreased BOLD signal while viewing sad facial expressions in the left anterior cingulate cortex (BA 6/24; $t(36) = -4.04, p<0.005$), left lingual gyrus (extending into fusiform cortex) (BA 18; $t(36) = -3.08, p<0.005$), right insula (BA 13; $t(36) = -4.03, p<0.005$), right cuneus (BA 17; $t(36) = -3.45, p<0.005$), left precuneus (BA 7; $t(36) = -3.12, p<0.005$), right superior frontal gyrus (BA 9; $t(36) = -3.27, p<0.005$), and right inferior parietal lobule (BA 40; $t(36) = -3.46, p<0.005$).

Emotional intensity contrast

We conducted an additional contrast to further explore the finding that bvFTD was associated with increased activity relative to controls in posterior parietal and posterior cingulate cortices during angry and happy facial expressions. Recent evidence implicates parietal regions in stabilizing goal-relevant stimuli that are not strongly represented, perhaps due to reduced afferent input from emotion-related brain regions (Amting et al., 2010). Accordingly, we hypothesized that increased activity in this dorsal network may reflect increased top-down efforts to enhance representation of faces in the ventral visual stream caused by reduced limbic input to this region in bvFTD patients. If so, we predicted that bvFTD patients would show augmented posterior parietal and posterior cingulate cortex activation during low emotional intensity faces when task demands are greatest relative to high emotional intensity faces, compared to controls. To test this hypothesis we examined differences between bvFTD patients and controls for both high emotional intensity (100%) and low intensity (40%) stimuli across all emotional expressions. During high intensity expression processing, bvFTD patients showed increased activity only in right inferior parietal lobule (BA 39; $t(36) = 3.24$, $p<0.005$) relative to controls. Consistent with our hypothesis, during low intensity emotional face processing bvFTD patients showed increased activation relative to controls in an expanded dorsal network including both right (BA 39; $t(36) = 3.84$, $p<0.005$) and left inferior parietal lobules (BA 39; $t(36) = 3.19$, $p<0.005$), left posterior cingulate cortex (BA 31; $t(36) = 3.07$, $p<0.005$) and left precuneus (BA 7; $t(36) = 3.03$, $p<0.005$) (Figure 2.6 and Table 2.4).

Table 2.3. Neural regions demonstrating significant BOLD differences between bvFTD patients and healthy controls during emotional face processing

Anatomical location	L/R	BA	Volume (mm^3)	Coordinates			*t* value
				x	y	z	
Angry expressions							
bvFTD < controls							
Inferior frontal gyrus	R	47	189	23	9	-22	-3.78
Amygdala**	L	NA	216	-23	0	-26	-2.11
Fusiform gyrus	L	37	675	-35	-51	-14	-3.18
Cuneus	R	17	324	23	-89	8	-3.43
bvFTD > controls							
Posterior cingulate cortex	L	31	351	-2	-46	26	3.12
Inferior parietal lobule	R	39	270	38	-62	32	3.66
Disgust expressions							
bvFTD < controls							
Insula	R	13	432	38	14	7	-3.21
Insula	L	13	270	-35	23	4	-3.49
Lingual/fusiform gyrus	L	18	324	-20	-73	-5	-3.41
Middle occipital gyrus	R	18	351	23	-89	11	-3.12
Happy expressions							
bvFTD < controls							
Amygdala*	L	NA	648	-26	-4	-26	-2.31
bvFTD > controls							
Inferior parietal lobule	R	39	432	41	-69	38	3.05
Fear expressions							
bvFTD < controls							
Medial frontal gyrus	L	6	270	-2	-4	52	-3.26
Lingual/fusiform gyrus	L	18	216	-5	-91	-17	-3.60
Middle occipital gyrus	L	18	216	-20	-92	11	-3.23
Cuneus	R	17	432	23	-89	8	-3.25
Sad expressions							
bvFTD < controls							
Anterior cingulate cortex	L	6/24	459	-2	7	51	-4.04

Lingual/fusiform gyrus	L	18	270	-17	73	-5	-3.08
Insula	R	13	243	44	-14	8	-4.03
Cuneus	R	17	324	23	-89	8	-3.45
Precuneus	L	7	324	-8	-81	44	-3.12
Superior frontal gyrus	R	9	297	32	49	35	-3.27
Inferior parietal lobule	R	40	297	41	34	34	-3.46

All regions corrected for whole brain voxel-wise grey matter. Displayed in the table are: hemispheric location (L = left; R = right), Broadmann's area (BA), volume, Montreal Neurological Institute coordinates at the centre of peak activation (x,y,z), and maximum activity (*t* value) for each significant cluster. Functional threshold at $p < 0.005$; $p < 0.05$, corrected; *$p < 0.05$; $p < 0.05$, small volume corrected; ** $p < 0.05$; uncorrected.

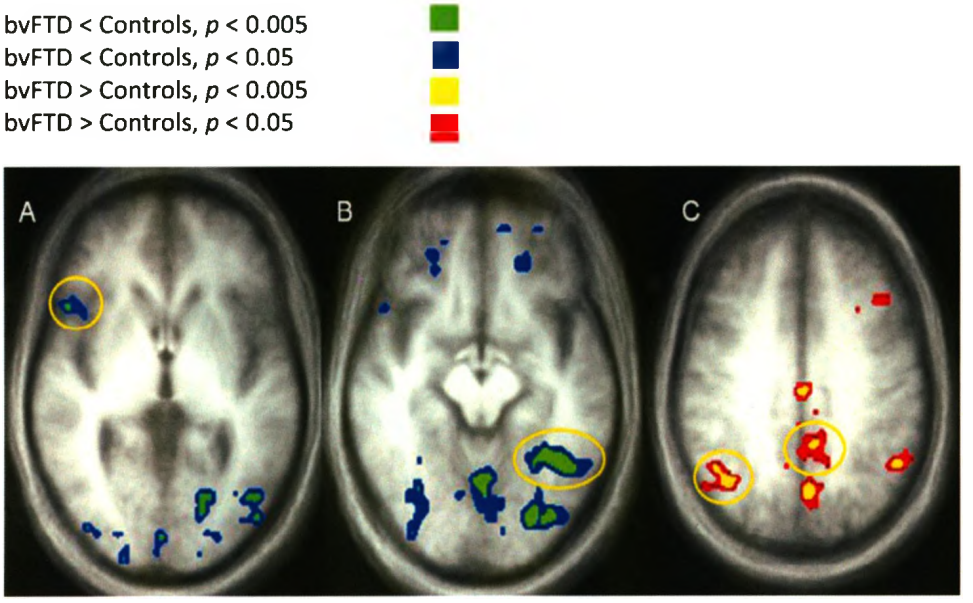

Figure 2.3. During angry expression processing, bvFTD patients demonstrated decreased BOLD signal (blue/green) compared to controls in (A) right ventrolateral prefrontal cortex and (B) ventral visual stream, specifically left fusiform gyrus. In contrast, bvFTD patients showed increased BOLD signal (red/yellow) in (C) right inferior parietal lobule and left posterior cingulate cortex. Significant clusters are shown at $p<0.005$ in yellow and green, and to illustrate the extent of the activations, at $p<0.05$ (uncorrected for multiple comparisons) in red and blue. Statistical maps are corrected for voxel-wise grey matter differences.

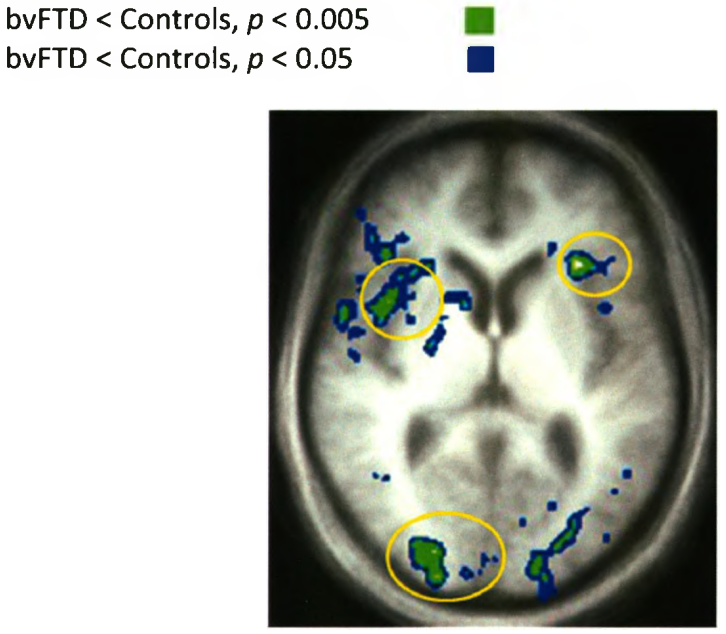

Figure 2.4. During disgusted expression processing, decreased BOLD signal (blue/green) in bilateral insula and right middle occipital gyrus is observed in bvFTD patients compared to controls. Significant clusters are shown at $p<0.005$ in green, and to illustrate the extent of the activation, at $p<0.05$ (uncorrected for multiple comparisons) in blue. Statistical map is corrected for voxel-wise grey matter differences.

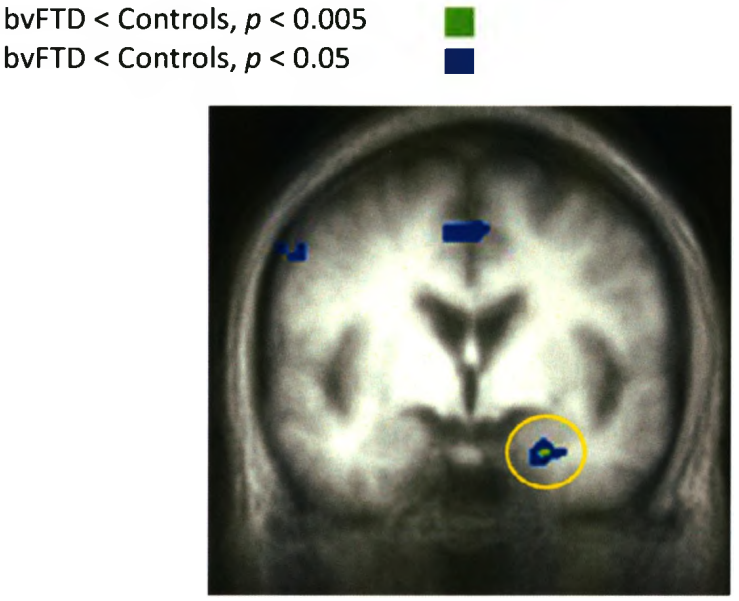

Figure 2.5. During happy expression processing, decreased BOLD signal (blue/green) in the left amygdala was observed in bvFTD patients relative to controls. Significant clusters are shown at $p<0.005$ in green, and at $p<0.05$ (uncorrected for multiple comparisons) in blue to show the full extent of the activation. Statistical map is corrected for voxel-wise grey matter differences.

Table 2.4. Neural regions demonstrating significant BOLD differences between bvFTD patients and healthy controls during facial expression processing of specific emotional intensities

Anatomical location	L/R	BA	Volume (mm^3)	Coordinates			*t* value
				x	y	z	
100% intensity							
bvFTD > controls							
Inferior parietal lobule*	R	39	189	38	-62	32	3.24
40% intensity							
bvFTD > controls							
Inferior parietal lobule	R	39	729	47	-65	35	3.84
Inferior parietal lobule*	L	39	54	2	12	46	3.19
Posterior cingulate cortex*	L	31	108	-5	-59	26	3.07
Precuneus *	L	7	81	-5	-65	35	3.03

All regions corrected for whole brain voxel-wise grey matter. Intensities for facial expressions are collapsed across emotions. Functional threshold at $p < 0.005$; $p < 0.05$, corrected. * $p < 0.005$; uncorrected.

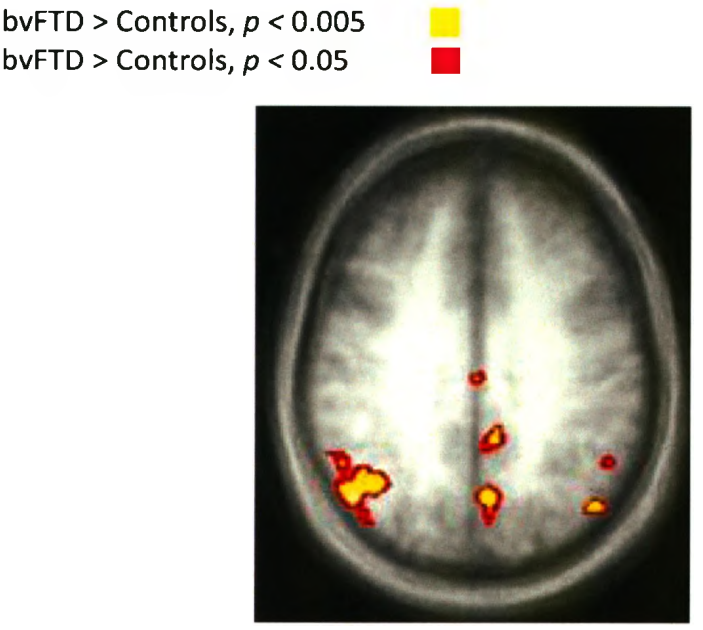

Figure 2.6. Contrast of low (40%) emotional intensity facial expressions in bvFTD patients compared to controls demonstrating increased BOLD signal (red/yellow) in bvFTD patients in a dorsal attentional network including bilateral inferior parietal lobule, left posterior cingulate cortex, and left precuneus. Significant clusters are shown at $p<0.005$ in yellow, and at $p<0.05$ (uncorrected for multiple comparisons) in red to illustrate the extent of activation. Statistical map is corrected for voxel-wise grey matter differences.

2.3.2.2 BvFTD patients without semantic deficits versus bvFTD patients with semantic deficits (Table 2.5)

In order to determine emotion-specific functional differences between bvFTD subtypes during facial expression processing we compared bvFTD patients without semantic deficits versus bvFTD patients with semantic deficits.

Anger

Relative to bvFTD patients with semantic deficits, bvFTD patients without semantic deficits demonstrated decreased BOLD signal in both right (BA 9; $t(18) = -3.38$, $p<0.005$) and left superior frontal gyrus (BA 8; $t(18) = -3.56$, $p<0.005$), and right middle frontal gyrus (BA 9; $t(18) = -3.81$, $p<0.005$) while viewing angry facial expressions.

Happy

Relative to bvFTD patients with semantic deficits, bvFTD patients without semantic deficits demonstrated decreased BOLD signal to happy faces in right medial frontal gyrus (BA 10; $t(18) = -3.38$, $p<0.005$), but increased BOLD signal in left amygdala ($t(18) = 2.65$, $p<0.05$) (Figure 2.7).

Sad

Relative to bvFTD patients with semantic deficits, bvFTD patients without semantic deficits demonstrated decreased BOLD signal in left anterior cingulate cortex (BA 24; $t(18) = -3.94$, $p<0.005$) and left medial frontal gyrus (BA 9; $t(18) = -3.38$,

$p<0.005$), but increased BOLD signal in left amygdala ($t(18) = 2.65, p<0.05$) while viewing sad facial expressions.

Fear

Relative to bvFTD patients with semantic deficits, bvFTD patients without semantic deficits demonstrated decreased BOLD signal to fearful faces in both right (BA 6; $t(18) = -3.45, p<0.005$) and left superior frontal gyrus (BA 6; $t(18) = -3.46, p<0.005$), left middle frontal gyrus (BA 6; $t(18) = -3.45, p<0.005$), and left precuneus (BA 7; $t(18) = -3.28, p<0.005$).

Disgust

No significant BOLD differences were found during disgusted expression processing between bvFTD patients with versus without semantic impairments.

Table 2.5. Neural regions demonstrating significant BOLD differences between bvFTD patients without semantic deficits and bvFTD patients with semantic deficits during emotional face processing

Anatomical location	L/R	BA	Volume (mm^3)	Coordinates			*t* value
				x	y	z	
Angry expressions							
bvFTD without semantic deficits < bvFTD with semantic deficits							
Superior frontal gyrus	L	8	1269	-17	46	44	-3.56
Superior frontal gyrus	R	9	1242	11	55	42	-3.38
Middle frontal gyrus	R	9	513	32	46	41	-3.81
Happy expressions							
bvFTD without semantic deficits < bvFTD with semantic deficits							
Medial frontal gyrus	R	10	351	20	45	-5	-3.38
bvFTD without semantic deficits > bvFTD with semantic deficits							
Amygdala*	L	NA	513	-17	-1	-11	3.26
Sad expressions							
bvFTD without semantic deficits < bvFTD with semantic deficits							
Anterior cingulate cortex	L	24	324	-2	22	27	-3.94
Medial frontal gyrus	L	9	216	-8	47	22	-3.38
bvFTD without semantic deficits > bvFTD with semantic deficits							
Amygdala**	L	NA	54	-20	-1	-15	2.65
Fear expressions							
bvFTD without semantic deficits < bvFTD with semantic deficits							
Superior frontal gyrus	L	6	837	-23	8	62	-3.46
Superior frontal gyrus	R	6	405	20	11	62	-3.45
Middle frontal gyrus	L	6	351	-17	-11	67	-3.45
Precuneus	L	7	432	-23	-54	55	-3.28
Disgust expressions							
None							

All regions corrected for whole brain voxel-wise grey matter. Functional threshold at $p < 0.005$; $p < 0.05$, corrected; *$p < 0.05$; $p < 0.05$, small volume corrected; ** $p < 0.05$; uncorrected.

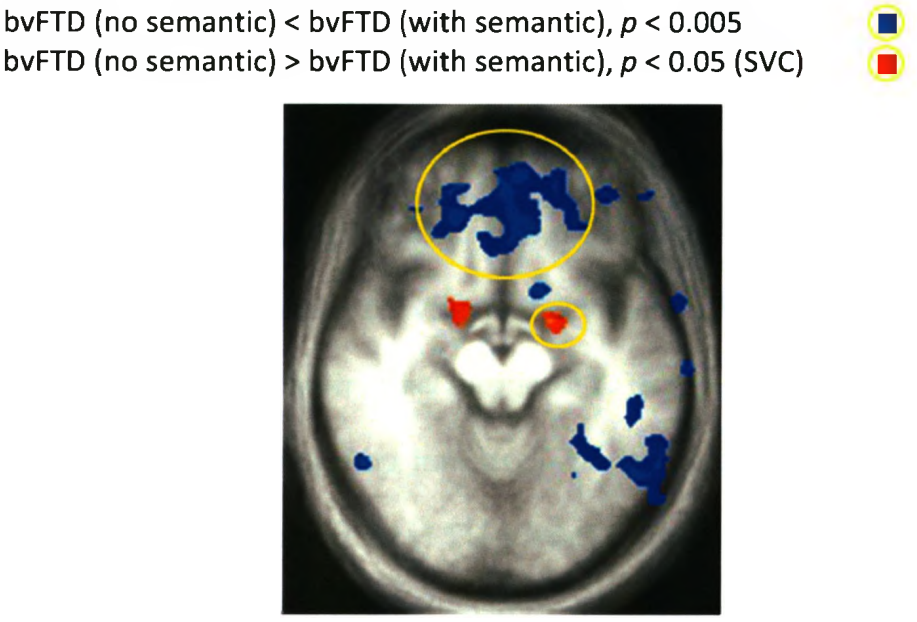

Figure 2.7. Contrasting bvFTD patients with and without semantic deficits during happy expression processing reveals significantly decreased BOLD signal (blue) in right medial frontal gyrus but increased BOLD signal (red) in the left amygdala in bvFTD patients without semantic deficits. Identified clusters are significant at $p< 0.005$ (except for the amygdala which is significant at $p<0.05$, small volume corrected). Statistical map is shown at $p<0.05$. Functional differences are corrected for voxel-wise grey matter differences.

2.4 Discussion

The current study used fMRI to delineate the emotion-specific neural correlates of implicit facial emotion processing in patients with bvFTD. We found that fMRI was sensitive in detecting emotion-specific changes in BOLD signal in bvFTD patients within frontotemporal regions previously implicated in the processing of specific emotions in healthy controls and affected by bvFTD pathology, even after correcting for measureable grey matter loss. Following our predictions, BOLD signal decreases were also observed in the ventral visual stream, a region not typically affected by bvFTD pathology, perhaps suggesting a functional disconnect between ventral visual cortices and frontal and limbic regions. The present results indicate that functional differences between bvFTD subtypes (those with and without semantic impairment) can be delineated using fMRI. Finally, increased activation was observed in bvFTD patients in a cortical network implicated in attentional processes, providing some of the first evidence to suggest that top-down compensatory mechanisms are recruited during cognitive processes in bvFTD.

2.4.1 Functional neural correlates of implicit emotional face processing in bvFTD

Prior studies of the neural correlates of emotion processing in FTD have focused exclusively on structural atrophy and found a limited number of associations. For example, reduced right inferolateral temporal cortex volume associated with deficits in negative emotion recognition (Rosen et al., 2006) and reduced posterior insula volume associated with anger recognition difficulties (Omar et al., 2010). In the present study, the use of fMRI during emotional stimuli processing demonstrated, for the first time, the

neural representation of emotional expressions in patients with bvFTD after controlling for structural abnormalities.

Considerable evidence suggests that a number of neural regions activated by emotional facial expressions are also active when one experiences the expression oneself (Carr et al., 2003; Leslie et al., 2004; Preston and de Waal, 2002; Wicker et al., 2003). This "mirroring" of another's emotional expressions is thought to generate internal representations of both the motor features as well as other regions relevant to the significance of the specific emotion (Budell et al., 2010; Carr et al., 2003). Supporting this model, bvFTD patients showed decreased BOLD activation within insular cortex in response to disgusted facial expressions, consistent with the known role of this region in normal disgust processing (Calder et al., 2007; Phillips et al., 1997; Sprengelmeyer et al., 1998), and in early bvFTD pathology (Seeley et al., 2008). Insula activation to disgusted faces may reflect the awareness of another's gustatory processes (Jabbi et al., 2007); thus, reduced insula activation to disgust likely underlies some patients' own insensitivity both towards this social cue and towards disgusting environmental stimuli (e.g. rotten or raw foods; Calder et al., 2007; Ikeda et al., 2002). When viewing angry faces, bvFTD patients demonstrated decreases in BOLD activation in ventrolateral prefrontal cortex. Previous work has associated ventrolateral prefrontal cortical activation with angry expression processing (Blair et al., 1999) and in modulating socially adaptive behaviour in response to social cues (Blair and Cipolotti, 2000; Finger et al., 2006; Marsh et al., 2009). Similarly, ventrolateral prefrontal cortex atrophy has been associated with inappropriate social behaviours in patients with FTD (Massimo et al., 2009). BvFTD patients showed decreased activation in the amygdala while viewing happy faces,

demonstrating the sensitivity of fMRI in detecting neural dysfunction for an emotion frequently correctly recognized by patients with bvFTD (Fernandez-Duque and Black, 2005). Counter to predictions, we did not find significant differences in the amygdala during fearful face processing despite the frequent association of this region with fearful face processing in healthy adults (Morris et al., 1996; Whalen et al., 1998). In the present study, this likely resulted from the lack of significant amygdala activation in the control participants during fearful faces. The reason for this lack of response in the controls is unclear, as prior studies using similar fearful facial expression stimuli with similar presentation parameters have reported increased amygdala activity in control participants when viewing fearful faces (Marsh et al., 2008; Morris et al., 1996). Furthermore, gender discrimination reaction times were not assessed; however, different reaction times between bvFTD patient and controls may potentially influence the BOLD signal as it may indicate different lengths of time engaging with the stimuli. Future analyses may benefit from including reaction time to further elucidate neural dysfunction during social-cognitive tasks in bvFTD.

Past correlations of atrophy patterns with recognition of emotional facial expressions have been insensitive in detecting significant differences between frontal-dominant and temporal-dominant FTD anatomical subtypes (Omar et al., 2010). We examined whether fMRI would be sensitive in delineating functional differences between bvFTD subtypes reflecting temporal versus frontal predominant pathologic patterns (presence or absence of semantic impairment) (Rosen et al., 2002a; Seeley et al., 2005) during facial expression viewing. Across several emotions, bvFTD patients without semantic deficits showed reduced activation in regions of prefrontal cortex compared to

those with semantic deficits. In contrast, bvFTD patients with semantic deficits demonstrated reduced activation in the amygdala for happy expressions. The present results indicate that fMRI with targeted cognitive tasks can reveal functional dissociations between these subtypes, providing support for the power of fMRI to delineate neural differences both between bvFTD and controls as well as between bvFTD subtypes.

Neuroimaging and lesion studies indicate that regions comprising the distributed neural face processing network communicate and influence each other, rather than functioning independently. Functional imaging studies in humans have demonstrated that ventral visual cortices, specifically lateral fusiform cortex, shows more activation for emotional (angry, happy, fearful, sad or disgusted) versus neutral faces (Amting et al., 2010; Fusar-Poli et al., 2009; Morris et al., 1998; Pessoa and Ungerleider, 2004; Vuilleumier et al., 2001), and for higher emotional intensities versus lower (Surguladze et al., 2003). Research suggests that projections from the amygdala modulate activity in the ventral visual stream, augmenting activation in fusiform cortex for emotionally salient stimuli (Amaral et al., 1992; Vuilleumier et al., 2001, 2004). While the amygdala responds to crude, low resolution aspects of emotional faces, the fusiform is implicated in processing features in higher resolution (Vuilleumier et al., 2003). In addition to fusiform cortex, other visual areas modulated by anterior frontal and limbic structures in response to emotional facial stimuli include posterior temporal cortex, occipital gyrus, cuneus, and lingual gyrus (Pessoa et al., 2002; Vuilleumier et al., 2001, 2004). Consistent with these models, we found that bvFTD patients demonstrated reduced activity in fusiform cortex and other ventral visual regions during the viewing of negative

emotional expressions (angry, fearful, disgusted, sad). Of interest, this pattern was not observed during happy expressions – the expression usually least affected in bvFTD (Fernandez-Duque and Black, 2005), despite our finding of reduced amygdala activity when viewing this emotion. We suggest that decreased activation in the ventral visual stream in bvFTD patients during negative emotional face processing is most likely due to reduced afferent inputs from more anterior frontotemporal and limbic regions. This hypothesis can be further explored in future studies via a functional connectivity analysis, where bvFTD patients would be predicted to demonstrate reduced correlated BOLD activation between ventral visual regions (specifically fusiform cortex) and limbic structures during facial expression viewing.

2.4.2 Top-down compensatory response in bvFTD as a function of emotional intensity

The current study provides some of the first evidence that at the neural level, patients with bvFTD may augment activity in regions not directly affected by FTD to compensate for their emotional impairment. Previous studies have demonstrated that emotion-related subcortical activity serves to boost stimulus representation in the ventral visual system in a "bottom-up" manner (Amting et al., 2010; Blair and Mitchell, 2009; Morris et al., 1998; Pessoa et al., 2002). Face perception tasks limiting ventral visual (bottom-up) input have detected increased associated frontoparietal (top-down) activity in the "dorsal attention network" (Tomasi and Volkow, 2011), including regions such as inferior parietal lobule, posterior cingulate cortex, dorsolateral prefrontal cortex, and precuneus (Amting et al., 2010; Kouider et al., 2009; Li et al., 2009). Indeed, a number of studies now show that frontoparietal activity increases with heightened demands

during a variety of cognitive processes including attention, decision-making, or rule-learning (Dumontheil et al., 2011; Mitchell, 2011; Mitchell et al., 2007, 2009). Activation of this dorsal attention network provides important contributions in conditions when bottom-up stimulus amplification is reduced during face processing (Amting et al., 2010), consistent with prior suggestions that attention enhances neural representation in category-specific regions (Desimone and Duncan, 1995). In the present study, bvFTD patients displayed increased activation compared to controls in a dorsal attentional network, including the inferior parietal lobules, posterior cingulate cortex, and precuneus for several of the emotional expressions. To further explore the hypothesis that this activity reflected top-down compensatory efforts to bolster facial expression processing in fusiform cortex in the absence of limbic modulation, we examined whether activity in this network was greater for the low emotional intensity compared to high intensity facial expressions. In both bvFTD patients and controls, high emotional intensity expressions would be expected to generate a greater limbic response compared to low intensity faces, leading to a reduced need for top-down compensation during the viewing of high intensity faces. Supporting this model, bvFTD patients recruited more of this dorsal attentional network when viewing low emotional intensity faces compared to less recruitment during high intensity expressions. This result provides the first evidence in bvFTD patients of a potential top-down attentional compensatory response during a social-cognitive task.

2.4.3 Limitations

When interpreting fMRI BOLD signal differences in neurodegenerative diseases, atrophy is a potential confound. Neural functional abnormalities, incorporating a volume correction into functional analyses, have previously been noted in resting state fMRI and arterial spin labeling MRI studies in FTD (Du et al., 2006; Zhou et al., 2010) and fMRI studies in Alzheimer's disease (Dickerson et al., 2005). Although voxel-based morphometry has demonstrated sensitivity in measuring volume differences during varied stages in bvFTD (Rosen et al., 2002a; Seeley et al., 2008; Whitwell et al., 2009), we cannot exclude the possibility that despite the atrophy correction, subtle differences in regional volumes, rather than neuronal dysfunction in the absence of atrophy, could account for the differences in BOLD signal between groups. An alternative route to correct for volume differences between groups would be to incorporate cortical thicknesses into the fMRI analysis, following the assumption that cortical thickness parallels bvFTD pathology; however, this analytical technique would encompass ROI fMRI analysis as opposed to whole brain voxel-wise analysis. Another potential limitation is the lack of definitive, autopsy confirmation of FTD in this cohort. Despite our clinical sample of bvFTD patients meeting revised criteria for bvFTD diagnosis (Rascovsky et al., 2010), autopsy confirmation of FTD is still pending, therefore, unintentional inclusion of patients with Alzheimer's disease or other diseases involving progressive frontal lobe dysfunction cannot be ruled out. However, as prior studies of patients with Alzheimer's disease have shown increased amygdala responses during facial expression processing (Wright et al., 2007), their inclusion would have been

expected to reduce power in the present study, and thus would be unlikely to account for these results.

2.5 Conclusions

In summary, we have demonstrated that fMRI coupled with an emotion processing task can demonstrate functional activation abnormalities in bvFTD and between bvFTD subtypes. For the first time, we have demonstrated the functional neural correlates of deficient emotion processing in patients with FTD. Given the relationship between the viewing of emotional expressions and one's own internal emotional experience, this approach offers an exciting means to objectively measure the internal emotional experience of patients with FTD. The results also show for the first time increased BOLD activation during task performance which may reflect top-down attentional compensatory efforts. The demonstration of these functional differences following atrophy correction, and comparisons to other voxel-based morphometry studies, suggests that measurable functional abnormalities exceed that of measurable atrophy and indicate that future use of fMRI combined with symptom-targeting tasks may be a powerful tool to detect early neural dysfunction before significant, irreversible atrophy is present.

2.6 References

Adolphs R, Tranel D, Damasio H, Damasio A. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 1994; 372: 669-72.

Amaral D, Price J, Pitkanen A, Carmichael S. Anatomical organization of the primate amygdaloid complex. In the amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction. J. Aggleton ed. New York: Wiley-Liss, 1992: 1-66.

Amting JM, Greening SG, Mitchell DG. Multiple mechanisms of consciousness: the neural correlates of emotional awareness. J Neurosci 2010; 30: 10039-47.

Blair R, Mitchell D, Peschardt K, Colledge E, Leonard R, Shine J, et al. Reduced sensitivity to others' fearful expressions in psychopathic individuals. Personality and individual differences 2004; 37: 1111-1122.

Blair RJ. Facial expressions, their communicatory functions and neuro-cognitive substrates. Philos Trans R Soc Lond B Biol Sci 2003; 358: 561-72.

Blair RJ, Cipolotti L. Impaired social response reversal. A case of 'acquired sociopathy'. Brain 2000; 123 (Pt 6): 1122-41.

Blair RJ, Mitchell DG. Psychopathy, attention and emotion. Psychol Med 2009; 39: 543-55.

Blair RJ, Morris JS, Frith CD, Perrett DI, Dolan RJ. Dissociable neural responses to facial expressions of sadness and anger. Brain 1999; 122 (Pt 5): 883-93.

Budell L, Jackson P, Rainville P. Brain responses to facial expressions of pain: emotional or motor mirroring? Neuroimage 2010; 53: 355-63.

Calder AJ, Beaver JD, Davis MH, van Ditzhuijzen J, Keane J, Lawrence AD. Disgust sensitivity predicts the insula and pallidal response to pictures of disgusting foods. Eur J Neurosci 2007; 25: 3422-8.

Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc Natl Acad Sci USA 2003; 100: 5497-502.

Corden B, Critchley HD, Skuse D, Dolan RJ. Fear recognition ability predicts differences in social cognitive and neural functioning in men. J Cogn Neurosci 2006; 18: 889-97.

Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 1996; 29: 162-73.

Darwin C. The expression of the emotions in man and animals. London: Albemarle, 1872.

Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci 1995; 18: 193-222.

Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, et al. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology 2005; 65: 404-11.

Diehl-Schmid J, Pohl C, Ruprecht C, Wagenpfeil S, Foerstl H, Kurz A. The Ekman 60 Faces Test as a diagnostic instrument in frontotemporal dementia. Arch Clin Neuropsychol 2007; 22: 459-64.

Du AT, Jahng GH, Hayasaka S, Kramer JH, Rosen HJ, Gorno-Tempini ML, et al. Hypoperfusion in frontotemporal dementia and Alzheimer disease by arterial spin labeling MRI. Neurology 2006; 67: 1215-20.

Dumontheil I, Thompson R, Duncan J. Assembly and use of new task rules in fronto-parietal cortex. J Cogn Neurosci 2011; 23: 168-82.

Eslinger PJ, Moore P, Anderson C, Grossman M. Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. J Neuropsychiatry Clin Neurosci 2011; 23: 74-82.

Fernandez-Duque D, Black SE. Impaired recognition of negative facial emotions in patients with frontotemporal dementia. Neuropsychologia 2005; 43: 1673-87.

Finch N, Baker M, Crook R, Swanson K, Kuntz K, Surtees R, et al. Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. Brain 2009; 132: 583-91.

Finger EC, Marsh AA, Kamel N, Mitchell DG, Blair JR. Caught in the act: the impact of audience on the neural response to morally and socially inappropriate behavior. Neuroimage 2006; 33: 414-21.

Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, et al. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 2009; 34: 418-32.

Haxby JV, Hoffman EA, Gobbini MI. The distributed human neural system for face perception. Trends Cogn Sci 2000; 4: 223-233.

Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain 1992; 115 (Pt 6): 1783-806.

Huey ED, Goveia EN, Paviol S, Pardini M, Krueger F, Zamboni G, et al. Executive dysfunction in frontotemporal dementia and corticobasal syndrome. Neurology 2009; 72: 453-9.

Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002; 73: 371-6.

Jabbi M, Swart M, Keysers C. Empathy for positive and negative emotions in the gustatory cortex. Neuroimage 2007; 34: 1744-53.

Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002; 17: 825-41.

Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. Med Image Anal 2001; 5: 143-56.

Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 1997; 17: 4302-11.

Keane J, Calder AJ, Hodges JR, Young AW. Face and emotion processing in frontal variant frontotemporal dementia. Neuropsychologia 2002; 40: 655-65.

Kertesz A, Blair M, McMonagle P, Munoz DG. The diagnosis and course of frontotemporal dementia. Alzheimer Dis Assoc Disord 2007; 21: 155-63.

Kouider S, Eger E, Dolan R, Henson RN. Activity in face-responsive brain regions is modulated by invisible, attended faces: evidence from masked priming. Cereb Cortex 2009; 19: 13-23.

Lavenu I, Pasquier F, Lebert F, Petit H, Van der Linden M. Perception of emotion in frontotemporal dementia and Alzheimer disease. Alzheimer Dis Assoc Disord 1999; 13: 96-101.

Leslie KR, Johnson-Frey SH, Grafton ST. Functional imaging of face and hand imitation: towards a motor theory of empathy. Neuroimage 2004; 21: 601-7.

Li J, Liu J, Liang J, Zhang H, Zhao J, Huber DE, et al. A distributed neural system for top-down face processing. Neurosci Lett 2009; 451: 6-10.

Lough S, Kipps CM, Treise C, Watson P, Blair JR, Hodges JR. Social reasoning, emotion and empathy in frontotemporal dementia. Neuropsychologia 2006; 44: 950-8.

Lund-Manchester. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry 1994; 57: 416-8.

Lundqvist D, Flykt A, Ohman A. The Karolinska Directed Emotional Faces (KDEF): Department of Clinical Neuroscience, Psychology Section, Karolinska Institutet, 1998.

Marsh AA, Blair KS, Jones MM, Soliman N, Blair RJ. Dominance and submission: the ventrolateral prefrontal cortex and responses to status cues. J Cogn Neurosci 2009; 21: 713-24.

Marsh AA, Blair RJ. Deficits in facial affect recognition among antisocial populations: a meta-analysis. Neurosci Biobehav Rev 2008; 32: 454-65.

Marsh AA, Finger EC, Mitchell DG, Reid ME, Sims C, Kosson DS, et al. Reduced amygdala response to fearful expressions in children and adolescents with

callous-unemotional traits and disruptive behavior disorders. Am J Psychiatry 2008; 165: 712-20.

Massimo L, Powers C, Moore P, Vesely L, Avants B, Gee J, et al. Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. Dement Geriatr Cogn Disord 2009; 27: 96-104.

McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001; 58: 1803-9.

Mitchell DG. The nexus between decision making and emotion regulation: a review of convergent neurocognitive substrates. Behav Brain Res 2011; 217: 215-31.

Mitchell DG, Luo Q, Avny SB, Kasprzycki T, Gupta K, Chen G, et al. Adapting to dynamic stimulus-response values: differential contributions of inferior frontal, dorsomedial, and dorsolateral regions of prefrontal cortex to decision making. J Neurosci 2009; 29: 10827-34.

Mitchell DG, Nakic M, Fridberg D, Kamel N, Pine DS, Blair RJ. The impact of processing load on emotion. Neuroimage 2007; 34: 1299-309.

Morris JS, Friston KJ, Buchel C, Frith CD, Young AW, Calder AJ, et al. A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain 1998; 121 (Pt 1): 47-57.

Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, et al. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 1996; 383: 812-5.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546-54.

Omar R, Rohrer JD, Hailstone JC, Warren JD. Structural neuroanatomy of face processing in frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry 2010.

Pessoa L, McKenna M, Gutierrez E, Ungerleider LG. Neural processing of emotional faces requires attention. Proc Natl Acad Sci USA 2002; 99: 11458-63.

Pessoa L, Ungerleider LG. Neuroimaging studies of attention and the processing of emotion-laden stimuli. Prog Brain Res 2004; 144: 171-82.

Phillips ML, Young AW, Scott SK, Calder AJ, Andrew C, Giampietro V, et al. Neural responses to facial and vocal expressions of fear and disgust. Proc Biol Sci 1998; 265: 1809-17.

Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, et al. A specific neural substrate for perceiving facial expressions of disgust. Nature 1997; 389: 495-8.

Preston SD, de Waal FB. Empathy: Its ultimate and proximate bases. Behav Brain Sci 2002; 25: 1-20; discussion 20-71.

Rankin, K, Kramer, BH, Miller, BL. Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. Cogn Behav Neurol 2005: 18: 28-36.

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, van Swieten JC, et al. Sensitivity of consensus diagnostic criteria in autopsy confirmed patients with behavioral variant frontotemporal dementia (bvFTD): First report of the

international bvFTD Criteria Consortium (FTDC). Dement Geriatr Cogn Disord 2010; 30.

Rohrer JD, Ahsan RL, Isaacs AM, Nielsen JE, Ostergaard L, Scahill R, et al. Presymptomatic generalized brain atrophy in frontotemporal dementia caused by CHMP2B mutation. Dement Geriatr Cogn Disord 2009; 27: 182-6.

Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 2002a; 58: 198-208.

Rosen HJ, Pace-Savitsky K, Perry RJ, Kramer JH, Miller BL, Levenson RW. Recognition of emotion in the frontal and temporal variants of frontotemporal dementia. Dement Geriatr Cogn Disord 2004; 17: 277-81.

Rosen HJ, Perry RJ, Murphy J, Kramer JH, Mychack P, Schuff N, et al. Emotion comprehension in the temporal variant of frontotemporal dementia. Brain 2002b; 125: 2286-95.

Rosen HJ, Wilson MR, Schauer GF, Allison S, Gorno-Tempini ML, Pace-Savitsky C, et al. Neuroanatomical correlates of impaired recognition of emotion in dementia. Neuropsychologia 2006; 44: 365-73.

Schneider W, Eschman A, Zuccolotto A. E-Prime user's guide. Pittsburgh: Psychology Software Tools, 2002.

Seeley WW, Bauer AM, Miller BL, Gorno-Tempini ML, Kramer JH, Weiner M, et al. The natural history of temporal variant frontotemporal dementia. Neurology 2005; 64: 1384-90.

Seeley WW, Crawford R, Rascovsky K, Kramer JH, Weiner M, Miller BL, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Arch Neurol 2008; 65: 249-55.

Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002; 17: 143-55.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004; 23 Suppl 1: S208-19.

Snowden JS, Goulding PJ, Neary D. Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 1989; 2:167-82.

Snowden JS, Neary D, Mann DM, Goulding PJ, Testa HJ. Progressive language disorder due to lobar atrophy. Ann Neurol 1992; 31: 174-83.

Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H. Neural structures associated with recognition of facial expressions of basic emotions. Proc Biol Sci 1998; 265: 1927-31.

Surguladze SA, Brammer MJ, Young AW, Andrew C, Travis MJ, Williams SC, et al. A preferential increase in the extrastriate response to signals of danger. Neuroimage 2003; 19: 1317-28.

Tomasi D, Volkow ND. Association between Functional Connectivity Hubs and Brain Networks. Cereb Cortex 2011.

Vuilleumier P, Armony JL, Driver J, Dolan RJ. Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron 2001; 30: 829-41.

Vuilleumier P, Armony JL, Driver J, Dolan RJ. Distinct spatial frequency sensitivities for processing faces and emotional expressions. Nat Neurosci 2003; 6: 624-31.

Vuilleumier P, Richardson MP, Armony JL, Driver J, Dolan RJ. Distant influences of amygdala lesion on visual cortical activation during emotional face processing. Nat Neurosci 2004; 7: 1271-8.

Warrington EK. The selective impairment of semantic memory. Q J Exp Psychol 1975; 27: 635-57.

Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci 1998; 18: 411-8.

Whitwell JL, Przybelski SA, Weigand SD, Ivnik RJ, Vemuri P, Gunter JL, et al. Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. Brain 2009; 132: 2932-46.

Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, Rizzolatti G. Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. Neuron 2003; 40: 655-64.

Winston JS, Henson RN, Fine-Goulden MR, Dolan RJ. fMRI-adaptation reveals dissociable neural representations of identity and expression in face perception. J Neurophysiol 2004; 92: 1830-9.

Woolley JD, Gorno-Tempini ML, Seeley WW, Rankin K, Lee SS, Matthews BR, et al. Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. Neurology 2007; 69: 1424-33.

Wright CI, Dickerson BC, Feczko E, Negeira A, Williams D. A functional magnetic resonance imaging study of amygdala responses to human faces in aging and mild Alzheimer's disease. Biol Psychiatry 2007; 62: 1388-95.

Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imaging 2001; 20: 45-57.

Zhou J, Greicius M, Gennatas E, Growden M, Jang J, Rabinovici G, et al. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. Brain 2010; 133: 1352-1367.

CHAPTER 3

Thesis conclusions

The objective of this thesis was to apply fMRI to index the emotion-specific neural correlates during implicit emotional face processing in bvFTD patients. This study reports fMRI to be sensitive in delineating the emotion-specific differences in BOLD signal between bvFTD patients and healthy matched controls within frontotemporal regions implicated in the healthy processing of facial expressions and affected by atrophy in bvFTD, even following a correction for measurable atrophy differences. Second, bvFTD was associated with decreased activation in ventral visual stream regions known to be involved in general face processing but not commonly affected in FTD, likely reflecting reduced afferent input from more anterior frontotemporal and limbic regions. Third, fMRI dissociated neural regions demonstrating functional differences during facial expression processing between bvFTD subtypes (presence or absence of semantic deficits) reflecting frontal versus temporal predominant atrophy patterns, demonstrating the greater potential of fMRI to elucidate neural abnormalities in FTD compared to previous structural correlation studies. Lastly, the results demonstrate increased activation in bvFTD patients in a top-down dorsal attentional network, indicating a potential compensatory neural response for impaired limbic system functioning. Importantly, as prior studies have demonstrated the similarity in neural activation patterns between viewing emotional facial expressions and experiencing the emotion oneself, the present results offer for the first time a potential objective quantification of the internal emotional experience in bvFTD. In totality, the combination of fMRI and social-cognitive targeted tasks may be a promising tool to

detect early neural dysfunction in bvFTD prior to significant atrophy progression, as well as to assess the efficacy of disease altering treatments. Future follow-up studies may benefit from scanning patients longitudinally to index the progression of neural dysfunction, including non-symptomatic biological family members of bvFTD patients to evaluate fMRI's power to detect neural dysfunction prior to disease symptom onset, and including other non-FTD neurodegenerative control groups (e.g. Alzheimer's disease) to assess the sensitivity of fMRI in dissociating bvFTD from other neurodegenerative diseases.

APPENDIX A

Subject medical history

	Medical History
Healthy Controls	
1	No neurologic disease or mental health problems. Taking diazepam. Taking Crestor and Tiazac for high blood pressure.
2	Not available.
3	Not available.
4	Not available.
5	No neurologic disease or mental health problems. Taking Pantoprazole for blood pressure.
6	Not available.
7	No reports of neurologic disease, mental health problems, or prescription medications for mood, depression, anxiety, insomnia, high blood pressure, or thyroid.
8	Not available.
9	No neurologic disease. Bipolar disorder. Taking epival (depakote) and indomethacin
10	Not available.
11	No reports of neurologic disease, mental health problems, or prescription medications for mood, depression, anxiety, insomnia, high blood pressure, or thyroid.
12	No reports of neurologic disease, mental health problems, or prescription medications for mood, depression, anxiety,

	insomnia, high blood pressure, or thyroid.
13	Not available.
14	Not available.
15	Not available.
16	Not available.
17	No reports of neurologic disease, mental health problems, or prescription medications for mood, depression, anxiety, insomnia, high blood pressure, or thyroid.
18	Not available.

bvFTD (no semantic deficits)

1	Previous pneumonia episode. Previous anxiety, panic attacks, and depression. Possible early diabetes.
2	No reports of neurologic disease (apart from FTD), mental health problems, or prescription medications for mood, depression, anxiety, insomnia, high blood pressure, or thyroid.
3	Substance abuse, starting in 2005.
4	Amyotrophic lateral sclerosis.
5	Not available.
6	Hypertension since 1967. Present anxiety treated with Effexor.
7	One possible visual hallucination. Diabetes. Reported episodes of passing out for about 5 minutes (no abnormality from Holter monitor).
8	Diabetes mellitus. Vertebral fracture in a fall with spinal fusion in 1977, resultant arthritis in spine, appendicitis with subsequent hernia through incision.
9	Possible mild depression during earlier age.
10	Diabetes. Hypertension. Hypothyroidism.

11	Diabetes mellitus. Hypertension. Sleep apnea.
12	Hypertension. Gastroesophageal reflux disease. Tinnitus. Hypercholesterolemia since 2009.

bvFTD (with semantic deficits)

1	Migraine-type headaches. Peptic ulcer disease. Back pain.
2	Seizures. A colloid cyst in the third ventricle of the brain. Hypertension. Hypercholesterolemia.
3	Hiatal hernia type 2 and nerve impingement in neck.
4	Diabetes. Hypercholesterolemia.
5	Hypercoagulability. Diabetes. High mercury and aluminum levels underwent chelation therapy. Hypertension. Pulmonary embolism (after a long trip).
6	History of skull fractures. Questionable depression at age 20. Second head injury with loss of consciousness at age 40 but no known hemorrhage or fracture. Developed industry-related deafness (progressive).
7	Hypertension. Hypercholesterolemia. Gastroesophageal reflux disease. Osteoarthritis. Chemical exposure to muriatic acid in 1996 (caused hospitalization for 6 weeks with lung damage and pneumonia).
8	Hypertension. Diabetes. Dyslipidemia.

APPENDIX B

Neuropsychological testing sample sizes

	Healthy controls /18	**bvFTD without SD** /12	**bvFTD with SD** /8
Education, years	18	12	8
Illness duration, years	NA	12	8
MMSE	15	12	7
FBI	NA	12	8
Immediate prose recall	15	12	6
Delayed prose recall	15	12	6
Letter fluency	15	12	5
Semantic fluency	15	12	5
Object naming	15	10	3
Spontaneous clock drawing	15	11	3
Clock copying	15	11	2
Beck Depression Inventory	15	9	0
Trails A	15	9	5
Trails B	15	6	1
ANART	15	9	4
WCST	15	8	4
Stroop A	15	11	3
Stroop B	14	11	2
Stroop C	14	11	2

APPENDIX C

Neuropsychological Test	Notes
MMSE	Cognitive impairment screen. Items include: time and place orientation, word (ball, flag, tree) and sentence repetition, delayed word recall (ball, flag, tree), backwards spelling (WORLD), naming objects, reading/doing "close your eyes", folding paper/place on floor, write a complete sentence, copying pentagons. Max = 30.
FBI	Inventory to quantify positive and negative behaviour and personality changes. Administered to caregivers. Useful adjunct in FTD diagnosis. Max = 72; sensitive FTD cutoff = 27.
Immediate prose recall	Participants are told a story regarding a fire, and are asked to recall the story immediately. Max = 21.
Delayed prose recall	Participants are asked to recall the fire story (from above) after a delay of twenty minutes. Max = 21.
Letter fluency	Participants are given 1 minute (for each letter) to name as many words beginning with 'F', 'A', or 'S'. Proper nouns (names, places) are not allowed. Total number of words across each category is summed.

Semantic fluency	Participants are given 1 minute to name as many animals as possible.
Object naming	Participants are to name 20 objects that are presented to them individually (e.g. plastic banana, safety pin). Objects that fail to be named without cues are subtracted from the total score. Max = 20.
Spontaneous clock drawing	Participants are asked to draw a clock, including all numbers, and set clock hands to "10 after 11". Drawings are scored based on contour, presence of all numbers, and proper hand location. Max = 10.
Clock copying	Participants shown a clock at 10 after 11 and asked to copy the clock. Max score = 10.
Beck Depression Inventory	Participants probed on feelings of sadness, distress, sleep cycles, etc. Higher score means higher depression rating. Max = 63.
Trails A	Participants draw a line connecting numbers in order (1 to 25). Score = number of seconds to complete path.
Trails B	Participants draw a line connecting number to letter, number to letter, in order, until path is complete. Score = number of seconds to complete path.
ANART	Involves correctly pronouncing a list of 50 words.

	Score = number of errors.
WCST	Participants shown 4 cards displaying shapes, which may vary in shape, colour, and number of shapes, and must correctly match a 5th card to one of the originally presented cards. Participants must decipher the matching principle (shape, colour, number) without any clues. Task consists of six principles, where participants must match 10 cards per principle to advance to the next principle. Max = 6.
Stroop A	Participants read as many words ("red", "blue", "green") as possible in 45 seconds.
Stroop B	Participants name the ink colour ("red", "blue", "green") of the presented words in 45 seconds.
Stroop C	Participants name the colour ("red", "blue", "green") of the ink of the words, with the ink colours being different than the colour denoted by the word, in 45 seconds.

APPENDIX D

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Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. E. Finger
Review Number: 13734 **Review Level:** Full Board
Review Date: November 6, 2007
Protocol Title: Investigating the Neurobiologic Etiologies of Behavioural and Cognitive Impairments in Frontotemporal Dementia
Department and Institution: Neurology, London Health Sciences Centre
Sponsor:
Ethics Approval Date: January 11, 2008 **Expiry Date:** October 31, 2012
Documents Reviewed and Approved: UWO Protocol, Letter of Information and Consent-Healthy Volunteers dated Dec 20, 2007, Letter of Information and Consent-Patients/Fam Members dated Dec 20, 2007, Letter of Information and Consent-Genetic Testing-Healthy Volunteers dated Dec 20, 2007, Letter of Information and Consent-Genetic Testing-Patient/Fam Members dated Dec 20, 2007
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. John W. McDonald

Ethics Officer to Contact for Further Information

☐ Janice Sutherland (jsutherland@uwo.ca)	☑ Jennifer McEwen (jmcewen4@uwo.ca)	☐ Grace Kelly (grace.kelly@uwo.ca)	☐ Denise Grafton (dgrafton@uwo.ca)

This is an official document. Please retain the original in your files.

cc: ORE File
LHRI